PT. Pfizer Indonesia
Local Product Document

Generic Name: Moroctocog alfa
Trade Name: XYNTHA
CDS Effective Date: January 18, 2019
Supersedes: NA

1. NAME OF THE MEDICINAL PRODUCT

XYNTHA

*Note: XYNTHA information applies to the product manufactured using the albumin-free process.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients

Moroctocog alfa (INN)

Physical characteristics

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

Single-use vial containing nominally 250, 500 or 1000 International Units (IUs) of moroctocog alfa (recombinant coagulation factor VIII).

3. PHARMACEUTICAL FORM

Single use vial:
Powder and solvent for solution for intravenous (IV) injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

XYNTHA is used for the control and prevention of hemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A (congenital factor VIII deficiency or classic haemophilia). (XYNTHA is appropriate for use in children of all ages.)

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

4.2. Posology and method of administration

Treatment with XYNTHA should be initiated under the supervision of a physician experienced in the treatment of haemophilia 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. Individual patients may vary in their response to factor VIII, achieving different levels of recovery and demonstrating different half-lives. Doses administered should be titrated to the patient's clinical response. In the presence of an inhibitor, higher doses or appropriate specific treatment may be required. Dosage adjustment for patients with renal or hepatic impairment has not been studied in clinical trials.

XYNTHA is appropriate for use in adults and children.

The number of units of factor VIII administered is expressed in IUs, 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 IUs (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 (% of normal or IU/dL) x 0.5 (IU/kg per IU/dL)

The labeled potency of XYNTHA is based on the European Pharmacopoeia chromogenic substrate assay in which the Wyeth manufacturing potency 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. With recombinant factor VIII products, clinical monitoring using the chromogenic assay typically yields results that are higher than the results obtained with the one-stage clotting assay.

Clinical data support the use of the one-stage clotting assay for monitoring XYNTHA therapy.

Based on their current regimen, individuals with haemophilia A should be advised to bring an adequate supply of factor VIII product for anticipated treatment when traveling. Patients should be advised to consult with their healthcare provider prior to travel.

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) outlined below for the indicated period.

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 12-24 hours as necessary, until resolved. At least 1 day, depending upon the severity of the hemorrhage.
Moderate		
Hemorrhages into muscles. Mild head trauma. 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 wound healing. 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 until adequate wound healing in the case of surgery; then therapy for at least another 7 days.

Dosage for prophylaxis

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

Inhibitors

Patients using factor VIII replacement therapy should be monitored for the development of factor VIII inhibitors. In patients with inhibitors (especially high level inhibitors, above 5 Bethesda units (BU)/mL), factor VIII therapy may not be effective, and other therapeutic options should be considered. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose testing should be performed to determine if a factor VIII inhibitor is present. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia. See also Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.

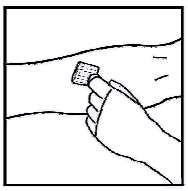
Administration

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

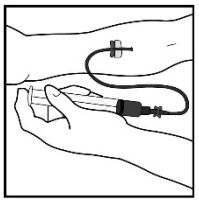
XYNTHA Antihemophilic Factor (Recombinant), Plasma/Albumin-Free should be administered using the infusion set provided in this kit and the pre-filled diluent syringe provided or a single sterile disposable plastic syringe. In addition, the solution should be withdrawn from the vial using the vial adapter.

1. Attach the syringe to the luer end of the infusion set tubing provided.

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



3. Perform venipuncture as instructed by your physician. Insert the needle on the infusion set tubing into the vein as instructed by your health care professional, and remove the tourniquet. Remove any air in the infusion set tubing by drawing back on the syringe. The reconstituted XYNTHA product should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.



Following completion of XYNTHA treatment, remove the infusion set and discard. Dispose of all unused solution, the empty vial(s), and the used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.

Paediatric population

Safety of XYNTHA was studied in previously treated children and adolescents (n=18, 12-16 years of age in a pivotal study and n=49, 7-16 years of age in a supporting study). In a pivotal study, adverse event data from patients who were ≤16 years of age were compared with data from those over 16 years of age. Eighteen (18) patients were ≤16 years of age and 76 were >16 years of age. Extent of exposure was similar for patients in the two age groups. Treatment emergent adverse events were similar in severity and incidence in the two age groups.

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

Elderly population

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

4.3. Contraindications

XYNTHA is contraindicated in patients with a known history of hypersensitivity to any of the constituents of the preparation and in patients with a known history of hypersensitivity to hamster proteins. XYNTHA has not been studied in patients with a known history of hypersensitivity to hamster proteins.

4.4. Special warnings and precautions for use

Hypersensitivity

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

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

Activity-neutralizing antibodies (inhibitors)

Activity-neutralizing antibodies (inhibitors) may develop in patients receiving coagulation factor VIII-containing products. As with all coagulation factor VIII products, patients should be monitored for the development of inhibitors that should be titrated in BUs using appropriate biological testing. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. See also Section 4.8 Undesirable effects.

These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in BUs using the Bethesda assay. The risk of developing inhibitors is correlated to the exposure to anti-hemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Inhibitors are common in previously untreated patients and have been observed in previously treated patients on factor VIII products.

Reports of lack of effect, mainly in prophylaxis patients, have been received in the clinical trials and in the post-marketing setting for ReFacto. The reported lack of effect with ReFacto has been described as bleeding into target joints, bleeding into new joints or a subjective feeling by the patient of new onset bleeding. When prescribing XYNTHA it is important to titrate and monitor each patient’s factor level in order to ensure an adequate therapeutic response. See also Sections 4.2 Posology and method of administration and 4.8 Undesirable effects.

It is recommended that, whenever possible, every time that XYNTHA is administered to patients, the name and batch number of the product is documented.

4.5. Interaction with other medicinal products and other forms of interaction

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

4.6. Fertility, pregnancy and lactation

Pregnancy

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

Lactation

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Adverse reactions to XYNTHA are listed in the table below. The information in this section is supported by the following studies: 300, 301, 306, 307, 310, 311, 313, 4432, 4433, and 4434.

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC (Per patient denominator)

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**
Blood and lymphatic system disorders	Factor VIII inhibition (PUPs)	Factor VIII inhibition (PTPs)	
Immune system disorders			Anaphylactic reaction
Metabolism and nutrition disorders		Decreased appetite	
Nervous system disorders	Headache	Dizziness	Dysgeusia; neuropathy peripheral; somnolence
Cardiac disorders			Angina pectoris; tachycardia; palpitations
Vascular disorders		Haemorrhage; haematoma	Hypotension; thrombophlebitis; flushing
Respiratory, thoracic and mediastinal disorders	Cough		Dyspnoea
Gastrointestinal disorders		Diarrhoea; vomiting; abdominal pain; nausea	

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Skin and subcutaneous tissue disorders		Urticaria; rash; pruritus	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Arthralgia	Myalgia	
General disorders and administration site conditions	Pyrexia	Chills; catheter site related reaction	Asthenia; injection site reaction; injection site pain; injection site inflammation
Investigations		Antibody test positive; anti-factor VIII antibody positive; human anti-mouse antibody positive[a]; liver function test abnormal	Blood creatinine phosphokinase increased

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

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently for ReFacto, and may in some cases progress to severe anaphylaxis (including shock).

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

Factor VIII inhibition

Previously treated patients

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

In a safety and efficacy clinical study in PTPs (study 310), the incidence of factor VIII inhibitors was the primary safety endpoint. Two clinically silent, low-titre, transient inhibitors were observed in 94 patients with a median exposure of 76 exposure days (ED, range 1-92), corresponding to 2.2% of the 89 patients with at least 50 ED. In a supporting study (study 306), 1 *de novo* and 2 recurrent inhibitors (all low-titre) were observed in 110 patients; median exposure of 58 ED (range 5-140) and 98 patients had at least 50 ED. Ninety-eight (98) of the original 110 patients continued treatment in a second supportive study (307) and had subsequent extended exposure with a median of 169 additional ED (range 9-425). One (1) additional low-

titre *de novo* inhibitor was observed. The frequency of inhibitors observed in these studies is within the expected range.

In a Bayesian statistical analysis, results from Study 310 were used to update PTP results from prior supporting studies. Two out of 89 subjects (who completed ≥50 exposure days) developed an inhibitor during the course of study 310. The observation of 2 inhibitors in 89 subjects who completed ≥50 exposure days was consistent with a 95% probability that the inhibitor formation rate is less than 4.17% using a Bayesian analysis.

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

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

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

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

Laboratory increases in anti-FVIII antibody titres, in the absence of inhibitor development, have been observed in clinical trials. In a study of PTPs for routine treatment and prevention of bleeding episodes (study 310) and in a study of PTPs for surgical prophylaxis (study 311), 1 of 94 (1%) patients, and 1 of 30 (3%) patients, respectively, developed anti-FVIII antibodies; these patients did not develop an inhibitor. The clinical significance of these antibodies, in the absence of an inhibitor, is unclear.

Previously untreated patients

In an earlier clinical trial using ReFacto (study 301), 32 out of 101 (32%) PUPs treated with ReFacto developed inhibitors: 16 out of 101 (16%) with a titre >5 BU/mL and 16 out of 101 (16%) with a titre ≤5 BU/mL. The median number of exposure days up to inhibitor development in these patients was 12 (range 3-49). Of the 16 patients with high titres, 15 received immune tolerance (IT) treatment. Of the 16 patients with low titres, IT treatment was started in 10. IT had an efficacy of 73% for patients with high titres and 90% for those with low titres. For all 101 treated PUPs, regardless of inhibitor development, the median number of exposure days is 197 (range 1-1299).

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

Trace amounts of hamster protein may be present in XYNTHA. Development of antibodies to hamster protein has been observed in clinical studies, but there were no associated clinical sequelae. In clinical trials of PTPs for routine treatment and prevention of bleeding episodes, 0 of 94 (0%) patients in study 310, and 3 of 110 (3%) patients in study 306/307, developed a lab increase in anti-CHO (Chinese hamster ovary, the cell line which is the source of factor VIII for XYNTHA) antibody titre, without any apparent clinical effect. In a study for surgical prophylaxis (study 311) 1 of 30 (3%) patients developed a lab increase for antibody to CHO. Twenty (20) of 113 (18%) PTPs receiving XYNTHA manufactured by the previous process (study 300) had an increase in anti-CHO antibody titre, without any apparent clinical effect.

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. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

4.9. Overdose

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

4.10. Abuse and dependence

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Antihemorrhagics: Blood Coagulation Factor VIII
ATC code: B02BD02

Mechanism of action

Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin, and a clot is formed. Factor VIII activity is greatly reduced in patients with haemophilia A, and therefore replacement therapy is necessary. The administration of XYNTHA increases plasma levels of factor VIII activity and can temporarily correct the coagulation defect in these patients.

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

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

Haemophilia A is an X chromosome-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendency.

Clinical trials data on efficacy

Pivotal data with XYNTHA:

In a pivotal phase 3 study, the efficacy of XYNTHA was evaluated in routine prophylaxis and on-demand treatment. Prophylaxis was to be initiated at a dose of 30 IU/kg given 3 times per week. The on-demand treatment dosing regimen was to be determined by the investigator. Ninety-four (94) PTPs with moderately severe or severe haemophilia A (FVIII:C ≤2%) received at least 1 dose of XYNTHA and were included in the intent-to-treat (ITT) population. Eighty-nine (89) patients accrued at least 50 exposure days (EDs) to XYNTHA in the study.

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

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

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

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

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

Additional data with Xyntha in paediatric population <16 years of age

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

Fifty-one (51) subjects with at least 20 prior EDs to FVIII products were enrolled and included in the intent-to-treat (ITT) population. Fifty (50) subjects received at least 1 dose of XYNTHA, and 41 subjects completed the study.

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

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

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

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

Forty-two (42) paediatric subjects <16 years of age received either routine prophylaxis dosing regimen 45 IU/kg twice per week or 25 IU/kg every other day for 12 months before crossing over to receive the alternate regimen, and 35 subjects provided data for both regimens. Because the 90% confidence interval (CI) for the difference of [(0.03, 2.22)] was inside the prospectively defined equivalence limit of (−3.3), equivalent efficacy was established with respect to ABR for both regimens (mean±SD 3.3±5.3 compared to 2.2±4.1).

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

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

5.2. Pharmacokinetic properties

ReFacto

Pharmacokinetic data were collected in 37 subjects at both baseline and Month 12 (Table 2) after ReFacto dosing. The 90% confidence intervals for the ratios of the mean values of Month 12-to-baseline AUC_T, AUC_∞, and recovery were well within the bioequivalence window of 80% to 125%, demonstrating the stability of these pharmacokinetic parameters over 1 year.

TABLE 2. MEAN FACTOR VIII PHARMACOKINETIC PARAMETERS FOR 37 PTPS FOLLOWING A RAPID INFUSION OF REFACTO AT A DOSE OF 50 IU/KG

Parameter	C_{max} (IU/ml)	AUC_t (hr*IU/ml)	Half-life (hr)	AUC_∞ (hr*IU/ml)	Clearance (ml/hr/kg)	Mean Residence Time (hr)	V_{ss} (ml/kg)	Recovery (IU/dl/IU/kg)
Baseline								
Mean	1.17	13.6	10.6	15.4	3.53	15.0	50.9	2.34
SD	0.24	3.4	2.5	4.5	1.03	3.4	13.0	0.49
Min	0.55	6.0	6.8	7.6	1.78	9.8	36.9	1.10
Max	1.90	21.1	17.2	28.1	6.60	24.7	99.0	3.80
Month 12								
Mean	1.20	14.0	11.4	16.5	3.37	16.1	51.1	2.40
SD	0.29	4.7	3.5	5.7	1.08	4.6	11.4	0.58
Min	0.84	7.8	6.6	8.8	1.49	9.7	21.3	1.67
Max	2.31	32.4	20.1	33.5	5.66	27.8	83.2	4.61

Abbreviations: AUC_∞=area under the plasma concentration-time curve from time zero to infinity; AUC_t=area under the plasma concentration-time curve from zero to the last measurable concentration; C_{max}=peak concentration; SD=standard deviation; V_{ss}=volume of distribution at steady-state.

Pharmacokinetic assessments have been conducted in PUPs. In PUPs (n=59; median age 10 ±

8.3 months), a mean recovery at Week 0 of 1.5 ± 0.6 IU/dl per IU/kg (range 0.2 to 2.8 IU/dl per IU/kg) was observed. Recovery was stable over a 2-year period and ranged from 1.5 to 1.8 IU/dl per IU/kg of ReFacto. Population pharmacokinetic modeling using data from 44 PUPs led to a mean estimated half-life 8.0 ± 2.2 hours. Compared with adults, the half-life of ReFacto is shorter in children and recovery is lower.

XYNTHA

The pharmacokinetic parameters for FVIII after XYNTHA were determined at baseline and followed-up in 25 previously treated patients (≥12 years) after repeated administration of XYNTHA for six months. No time-dependent changes in the pharmacokinetic properties of XYNTHA were observed (Table 3).

TABLE 3. MEAN FACTOR VIII PHARMACOKINETIC PARAMETERS FOR 25 PTPS FOLLOWING A RAPID INFUSION OF XYNTHA AT A DOSE OF 50 IU/KG

Parameter	C_{max} (IU/mL)	AUC_t (hr*IU/mL)	Half-life (hr)	AUC_∞ (hr*IU/mL)	Clearance (mL/hr/kg)	Mean Residence Time (hr)	V_{ss} (mL/kg)	Recovery (IU/dL/IU/kg)
Baseline								
Mean	1.12	13.3	11.8	14.2	4.21	16.3	65.1	2.23
SD	0.19	5.2	5.1	5.5	2.08	5.9	35.1	0.39
Min	0.59	4.1	6.4	4.7	2.00	7.9	34.8	1.19
Max	1.41	23.6	33.9	25.0	10.63	40.0	195.1	2.83
Month 6								
Mean	1.24	13.3	11.8	15.0	4.04	19.5	67.4	2.47
SD	0.42	6.7	6.2	7.5	1.87	16.1	32.6	0.84
Min	0.65	5.0	5.8	5.3	1.19	7.6	18.5	1.29
Max	2.60	41.0	32.6	14.8	9.45	89.2	168.8	5.20

Abbreviations: AUC_∞=area under the plasma concentration-time curve from time zero to infinity; AUC_t=area under the plasma concentration-time curve from zero to the last measurable concentration; C_{max}=peak concentration; SD=standard deviation; V_{ss}=volume of distribution at steady-state.
Reference: Table 16.20, CSR-66997

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 to 5.8 years after XYNTHA administration. Compared with adults, the half-life of factor VIII after XYNTHA is shorter in children and clearance (based on body weight) is approximately 40% higher in children.

TABLE 4. MEAN ± FVIII PHARMACOKINETIC PARAMETERS IN PREVIOUSLY TREATED PAEDIATRIC PATIENTS WITH HAEMOPHILIA A AFTER 50 IU/kg XYNTHA		
Parameter	Young Children (n=5)	Adolescents (n=4)
Age [(min–max) yr]	3.7 – 5.8	14 - 15
Cmax (IU/mL)	0.78 ± 0.34	0.97 ± 0.21
AUC_{∞} (IU.hr/mL)	12.2 ± 6.50	8.5 ± 4.0
t½ (hr)	8.3 ± 2.7	6.9 ± 2.4
CL (mL/hr/kg)	6.29 ± 4.87	6.62 ± 2.16
Vss (mL/kg)	66.9 ± 55.6	67.1 ± 13.6
Recovery (IU/dL/IU/kg)	1.52 ± 0.69	1.95 ± 0.41

Abbreviations: AUC_{∞}=area under the plasma concentration-time curve from time zero to infinity; C_{max}=peak concentration; $t_{½}$ = terminal half life; CL = clearance; V_{ss}=volume of distribution at steady-state.

5.3. Preclinical safety data

In preclinical studies, the predecessor product ReFacto was used to safely and effectively restore hemostasis. ReFacto and plasma derived factor VIII demonstrated similar toxicological profiles when tested in repeated dose toxicology studies in animals.

ReFacto shows no genotoxic properties in the mouse micronucleus assay. No other mutagenicity studies and no investigations on carcinogenesis, impairment of fertility or fetal development have been conducted.

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

In preclinical studies, XYNTHA was used to safely and effectively restore hemostasis. XYNTHA demonstrated a toxicological profile that was similar to the toxicological profile observed with the predecessor product ReFacto, which had in turn been shown to demonstrate a similar toxicological profile to a plasma-derived factor VIII product when tested in repeated dose toxicology studies in animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

<u>Powder</u>
Sucrose
Calcium chloride dihydrate
L-Histidine

Polysorbate 80
Sodium chloride

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

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.

6.4. Special precautions for storage

Product as packaged for sale: XYNTHA should be stored under refrigeration at a temperature of 2° to 8°C (36° to 46°F). Within the expiration date, XYNTHA may also be stored at room temperature not to exceed 25°C (77°F) for one single period up to 3 months. The patient should write in the space provided on the outer carton the date the product was placed at room temperature. At the end of the 3-month period, the product should not be put back into the refrigerator, but should be used immediately or discarded. The diluent syringe may be stored at 2° to 25°C (36° to 77°F). Freezing should be avoided to prevent damage to the pre-filled diluent syringe. During storage, avoid prolonged exposure of XYNTHA vial to light.

6.5. Nature and contents of container

XYNTHA 250 IU, 500 IU, 1000 IU powder and solvent for solution for injection
250 IU, 500 IU, 1000 IU powder in a 10 mL vial (type 1 glass) with a stopper (butyl) and a flip-off seal (aluminum) and 4 mL of solvent in a pre-filled syringe (type 1 glass) with a plunger stopper (butyl), a tip-cap (butyl) 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 250 IU, 500 IU, 1000 IU powder and solvent for solution for injection.
The vial of lyophilised product powder for injection must be reconstituted with the supplied solvent [sodium chloride 9 mg/mL (0.9%) solution] from the pre-filled syringe using the sterile vial adapter reconstitution device. The vial should be gently rotated until all of the powder is dissolved.

After reconstitution, the solution is drawn back into the syringe. The solution will be clear or slightly opalescent and colourless. The solution is to be discarded if visible particulate matter or discolouration is observed.

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.

Single use vial

Reconstitution

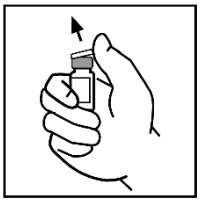
Always wash your hands before performing the following procedures. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure. All components used in the reconstitution and administration of this product should be used as soon as possible after opening their sterile containers to minimize unnecessary exposure to the atmosphere.

XYNTHA Antihemophilic Factor (Recombinant), Plasma/Albumin-Free is administered by intravenous (IV) infusion after reconstitution with the supplied diluent (0.9% Sodium Chloride solution) syringe.

> **Note**: If you use more than one vial of XYNTHA per infusion, each vial should be reconstituted as per the following instructions. The diluent syringe should be removed, leaving the vial adapter in place, and a separate, single large luer lock syringe may be used to draw back the reconstituted contents of each of the individual vials. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.

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

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

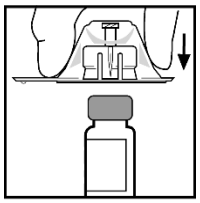


3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to

touch any surface.

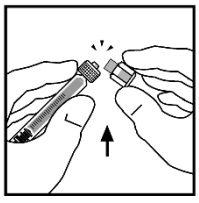
4. Peel back the lid from the clear plastic vial adapter package. Do not remove the adapter from the package.

5. Place the vial on a flat surface. While holding the adapter package, place the vial adapter over the vial and press down firmly on the package until the adapter spike penetrates the vial stopper. Leave the adapter package in place.

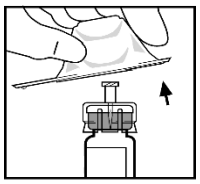


6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe by inserting the rod into the opening in the syringe stopper and pushing and turning the rod firmly until it is secured in the stopper.

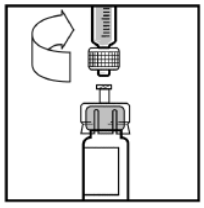
7. Break off the tamper-resistant plastic tip cap from the diluent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted XYNTHA immediately), so set the cap aside by placing it on its top.



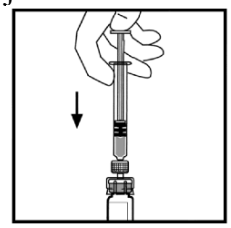
8. Lift the package away from the adapter and discard the package.



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.



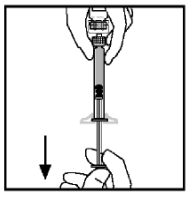
10. Slowly depress the plunger rod to inject all the diluent into the XYNTHA vial.



11. Without removing the syringe, gently rotate the vial until the powder is dissolved.

    Note: The final solution should be inspected visually for particulate matter before administration. The solution should appear clear to slightly opalescent 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 and slowly draw back all the solution through the vial adapter into the syringe.



13. Detach the syringe from the vial adapter by gently pulling and turning the syringe counter-clockwise. Discard the vial with the adapter attached.

    Note: If the solution is not to be used immediately, the syringe cap should be carefully

replaced. Do not touch the syringe tip or the inside of the cap.

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

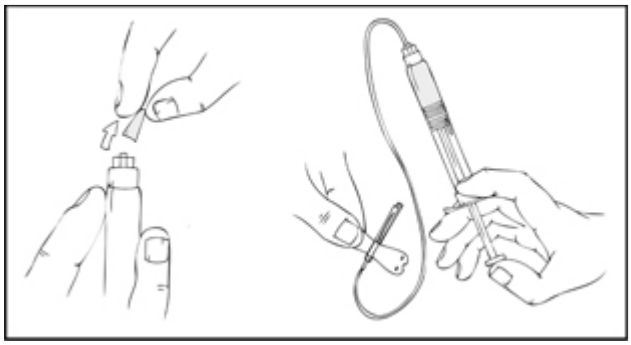
Administration (Intravenous Infusion)

Your doctor or other healthcare professional should teach you how to infuse XYNTHA. Once you learn how to self-infuse, you can follow the instructions in this Package Leaflet.

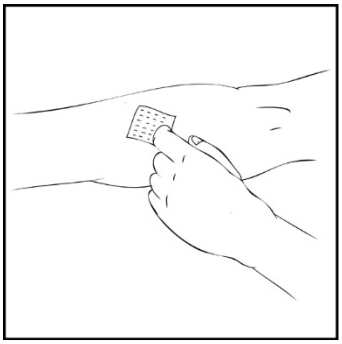
XYNTHA is administered by intravenous (IV) infusion after reconstitution of the powder with the solvent (0.9% sodium chloride). Once reconstituted, XYNTHA should be inspected for particulate matter and discolouration prior to administration.

XYNTHA should be administered using the infusion set included in the kit, unless otherwise advised by your doctor or other healthcare professional.

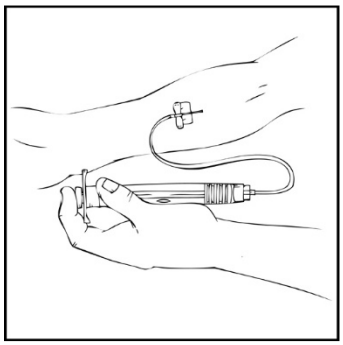
1. Remove the protective blue vented cap and firmly attach the intravenous infusion set provided onto the XYNTHA pre-filled syringe.



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



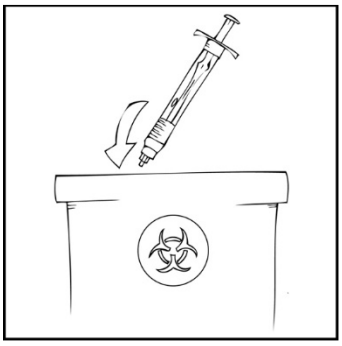
3. Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein, as instructed by your doctor or other healthcare professional. Remove the tourniquet. The reconstituted XYNTHA product should be injected intravenously over several minutes. Your doctor may change your recommended infusion rate to make the infusion more comfortable. Discuss your intravenous infusion procedure with your doctor or other healthcare professional. Do not attempt self-infusion unless properly trained.



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

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

Note: Please dispose of all unused solution, the empty pre-filled syringe, and the used medical supplies in an appropriate container for throwing away medical waste, as these materials may hurt others if not disposed of properly.



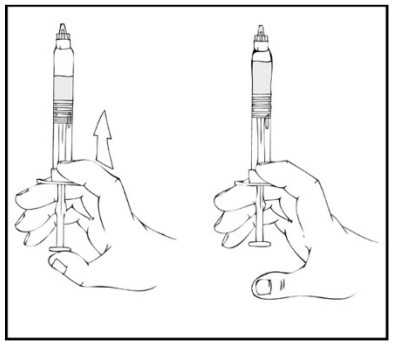
It is recommended to record the lot number from the XYNTHA pre-filled syringe label every time you use XYNTHA. You can use the peel-off label found on the XYNTHA pre-filled syringe to record the lot number.

- **Additional Instructions:**
- **Multiple XYNTHA in Pre-filled Syringe Reconstitution to a 10 cc or Larger Luer Lock Syringe (10 cc or larger luer lock syringes not provided)**

The instructions below are for the use of multiple XYNTHA pre-filled syringe kits with a 10 cc or larger luer lock syringe.

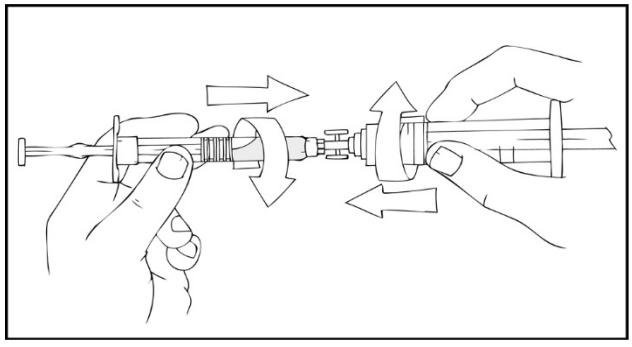
1. Reconstitute all XYNTHA pre-filled syringes according to instructions shown above in the reconstitution directions (see Reconstitution and Administration).

   Holding the XYNTHA pre-filled syringe in an upright position, slowly advance the plunger rod until most, but not all, of the air is removed from the drug product chamber.

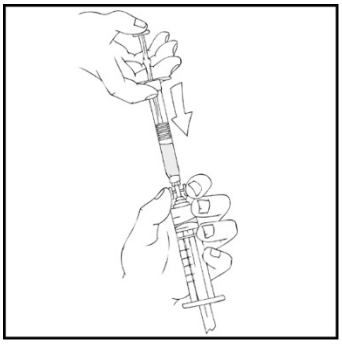


2. Remove the luer-to-luer syringe connector from its package (luer-to-luer syringe connectors are not provided).

3. Connect a sterile 10 cc or larger luer lock syringe to one opening (port) in the syringe connector and the XYNTHA pre-filled syringe to the remaining open port on the opposite end.



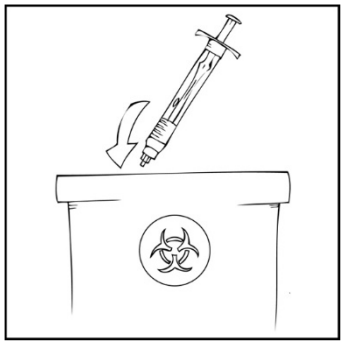
4. With the XYNTHA pre-filled syringe on top, slowly depress the plunger rod until the contents empty into the 10 cc or larger luer lock syringe.



5. Remove the empty XYNTHA pre-filled syringe and repeat procedures 3 and 4 above for any additional reconstituted syringes.

6. Remove the luer-to-luer syringe connector from the 10 cc or larger luer lock syringe and attach the infusion set, as described above in the directions for administration of the pre-filled syringe [see Administration (Intravenous Infusion)].

Note: Please dispose of all unused solution, the empty pre-filled syringe, and the used medical supplies in an appropriate container for throwing away medical waste, as these materials may hurt others if not disposed of properly.



Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
Wyeth Farma, S.A.
Autovía del Norte A-1 Km 23.
Desvio Algete, Km 1
28700 San Sebastian de los Reyes
Madrid, Spain

Diluent:

Manufactured by:
Vetter Pharma-Fertigung GmbH & Co.KG, Langenargen, Germany
Vetter Pharma-Fertigung GmbH & Co.KG, Ravensburg, Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER(S)

XYNTHA 250 IU; Box, 1 vial @ 250 IU + 1 pre-filled syringe @ 4 mL + 1 vial adapter + 1 sterile infusion set + 2 alcohol swabs + 1 plaster + 1 gauze; No. Reg.: DKI2158800144A1.
XYNTHA 500 IU; Box, 1 vial @ 500 IU + 1 pre-filled syringe @ 4 mL + 1 vial adapter + 1 sterile infusion set + 2 alcohol swabs + 1 plaster + 1 gauze; No. Reg.: DKI2158800144B1.
XYNTHA 1000 IU; Box, 1 vial @ 1000 IU + 1 pre-filled syringe @ 4 mL + 1 vial adapter + 1 sterile infusion set + 2 alcohol swabs + 1 plaster + 1 gauze; No. Reg.: DKI2158800144C1.

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

Sep 2025