ORIGINAL ARTICLE

BDDrFVIII (Moroctocog alfa [AF-CC]) for surgical haemostasis in patients with haemophilia A: results of a pivotal study

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Summary. Moroctocog alfa (AF-CC) (Xyntha™, BDDrFVIII) is manufactured by a process designed to enhance the theoretical viral safety profile relative to ReFacto®, its predecessor, and to provide alignment with clinical monitoring by the one-stage clotting assay. To evaluate the efficacy and safety of B-domain-deleted recombinant factor VIII (BDDrFVIII) was given as bolus injection (BI) or continuous infusion (CI) in haemophilia patients undergoing major surgery. BDDrFVIII was administered by BI or CI per investigator discretion perioperatively for at least 6 days. Thirty patients enrolled and were treated with at least one dose of BDDrFVIII. Twenty-five patients were evaluable for efficacy. Outcomes were favourable against a background of multiple major surgical procedures. All haemostatic efficacy ratings were ‘excellent’ or ‘good’. End-of-surgery haemostasis ratings, the primary efficacy endpoint, were excellent for 72% (18/25) and good for 28% (7/25) of patients. Haemostasis ratings following the initial postoperative period were excellent for 92% (23/25) and good for 8% (2/25) of patients. Intra-operative blood loss was rated as normal in all patients. Thirteen patients had postoperative blood loss; in 10, this was rated as normal. A low frequency of transfusion was reported in both the intra-operative and postoperative settings. Adverse events (AEs) were consistent with surgery; three were considered related to BDDrFVIII. One patient had a related AE of postoperative haemorrhage. A clinically silent low-titre inhibitor was detected in one patient, and one patient had a false-positive inhibitor titre. This study demonstrates that BDDrFVIII is safe and efficacious for surgical prophylaxis in haemophilia A patients undergoing major surgery.

Keywords: B-domain-deleted factor VIII, bolus injection, continuous infusion, factor VIII inhibitors, haemophilia A, surgical haemostasis

Introduction

Improvements in the manufacture of recombinant factor VIII (rFVIII) have been intended to reduce the risk of transmitting viral infection and to increase ease of use. Moroctocog alfa (AF-CC) (Xyntha™, BDDrFVIII) is a B-domain-deleted recombinant factor VIII (BDDrFVIII) manufactured by a process that has been modified to enhance the theoretical viral safety profile relative to predecessor product, ReFacto® [1].

In addition, the method for assignment of potency for this preparation of BDDrFVIII has been aligned with the one-stage clotting assay, thereby harmonizing the labelled potency of the drug with routine clinical monitoring using the one-stage clotting assay [2]. Previous studies have demonstrated that BDDrFVIII is safe and effective in the prevention and treatment of haemorrhages and has pharmacokinetic (PK) equivalence to full-length rFVIII [2].

Factor VIII (FVIII) replacement therapy is critical in maintaining haemostasis in patients with haem-
Haemophilia A undergoing surgery. This is usually achieved by administering FVIII concentrate during the surgical and postsurgical periods, until wound healing has been completed. Typically, replacement therapy is administered by bolus injections (BI); however, reports suggest that administration by continuous infusion (CI) may be associated with reduced requirements for FVIII concentrate and less fluctuation in FVIII activity plasma levels [3–8]. This open-label study was conducted to assess the safety and efficacy of BDDrFVIII administered by either BI or CI for the management of surgical haemostasis in patients with severe and moderately severe haemophilia A undergoing elective major surgery.

Materials and methods

This was a phase 3, open-label, multicentre, prospective study performed at a total of 13 study sites in seven countries, including the United States, New Zealand, Russia, Sweden, Austria, Poland and Romania.

The study was designed in accordance with the suggestions provided by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) and conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. All patients provided written informed consent/assent prior to surgery.

Patients

At least 25 patients were to be enrolled, including 12 to be treated by CI. All patients were to be men ≥12 years of age with severe or moderately severe haemophilia A undergoing elective major surgery that was anticipated to require rFVIII infusions with monitoring for at least 6 days after surgery. Major surgery was defined as surgery involving open abdominal, intracranial, orthopaedic, retroperitoneal, thoracic, pharyngeal, or retropharyngeal procedures, or invasive dental procedures involving complicated extractions.

Inclusion criteria included FVIII concentration (FVIII:C) ≤2%, negative assays for FVIII inhibitor at both local and central laboratories at screening, a negative history of a FVIII inhibitor and ≥150 prior exposure days to treatment with any FVIII product. Patients were to have adequate liver and kidney function, prothrombin time ≤1.25 times the upper limit of normal or international normalized ratio ≤1.5 and an absolute CD4 count >200 cells µL⁻¹. Patients being treated for human immunodeficiency virus (HIV) had to be on a stable antiviral regimen. Exclusion criteria included a bleeding disorder in addition to haemophilia A, regular use of antifibrinolytic agents or other agents known to influence platelet function and concomitant therapy with immunosuppressive drugs.

Study design and treatment

Patients were designated to receive BDDrFVIII by either BI or CI by the investigator at screening based on investigator preference and local treatment practices. At baseline (approximately 4 weeks before surgery), following a 3-day washout of all FVIII products, a 50 IU kg⁻¹ infusion of BDDrFVIII was administered for a recovery assessment in BI patients and for PK assessment in CI patients to estimate recovery and clearance rate, respectively. Investigators reported their target FVIII activity level for surgery and used results from the baseline assessments to plan the initial BDDrFVIII dose and injection frequency (BI) or infusion rate (CI). Patients returned to their usual FVIII replacement therapy regimen after this assessment until the day of surgery.

On the day of surgery, all patients received a bolus loading dose of BDDrFVIII to achieve the previously planned target plasma level of FVIII:C. Blood samples were obtained before and after the loading dose to determine levels of FVIII:C. Patients treated by CI began a BDDrFVIII infusion approximately 30 min after the start of the loading dose. Supplemental bolus doses (BI and CI) or rate adjustments (CI) could be made during the intra-operative period to account for possible variation in recovery and/or to account for individual variation from the expected clearance if needed, based on subsequent determinations of FVIII:C.

For administration by CI, BDDrFVIII was prepared based upon the results from Neidhardt et al. [9]. Large volume preparations were prepared with a final BDDrFVIII concentration of ≥10 IU mL⁻¹ resuspended in either 5% dextrose solution or normal saline, with minimum flow rates of 6 or 20 mL h⁻¹ respectively. Small doses of heparin (2–6 IU heparin mL⁻¹ of infusate) could be added to the solution to assist the administration of CI.

Patients received BDDrFVIII for ≥6 consecutive postoperative days (initial postoperative period) by BI or CI depending on the investigator-assigned treatment. Inpatient postoperative care had to be ≥2 days for BI patients and ≥6 days for CI patients;
daily assessments at the study site were required during the first 6 days after surgery for all patients. During the initial postoperative period, preinfusion blood samples for FVIII:C were obtained approximately 15 min before BI at least once daily. For CI patients, FVIII:C was measured and recorded each day during infusion. If FVIII:C did not sufficiently approximate the target level, additional BI could be administered for BI patients, or for CI patients, the infusion rate could be adjusted accordingly. For CI patients, supplemental BIs could be used in conjunction with CI at the investigator’s discretion to acutely correct the FVIII:C to the predetermined target level. Any bleeding episodes occurring during either the initial (first 6 postoperative days or period until discharge, whichever occurred later) or final postoperative period (remainder of treatment period up to a total of 6 weeks) were to be treated with an on-demand infusion(s) of BDDrFVIII.

During the final postoperative period, patients could continue postsurgical treatment with BDDrFVIII administered by BI on an outpatient basis for a total of up to 6 weeks. The final study visit was conducted at the end of this period, after which the patients could return to their respective presurgical regimens of commercially available FVIII replacement therapy. Approximately 4 weeks after the final visit, the patient completed the study activities with a final study contact.

Endpoints and assessments

The primary endpoint was haemostatic efficacy during the surgical procedure through 1 h after surgery completion (referred to as end of surgery), as assessed by the investigator or surgeon. The assessment was based on comparison to experience with similar patients undergoing similar procedures, using the four-point Surgical Hemostasis Efficacy Rating Scale (Table 1).

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<tr>
<th>Rating</th>
<th>Criteria</th>
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<tr>
<td>Excellent</td>
<td>Achieved haemostasis comparable to that expected after similar surgery in a patient without haemophilia</td>
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<tr>
<td>Good</td>
<td>Prolonged time to haemostasis, with somewhat increased bleeding compared with that expected after similar surgery in a patient without haemophilia</td>
</tr>
<tr>
<td>Moderate</td>
<td>Obviously delayed haemostasis, but manageable with additional infusions</td>
</tr>
<tr>
<td>None</td>
<td>No haemostatic response</td>
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Secondary efficacy endpoints were the four-point Surgical Hemostasis Efficacy Scale rating as assessed on postoperative day 7 for previously discharged BI patients or the day of hospital discharge for other patients; the total consumption of BDDrFVIII and consumption per bleeding event; the number of bleeding episodes and the efficacy of BDDrFVIII in treating the episode using a previously described four-point scale [2]; the comparison of the predicted and actual blood loss and transfusions and the PK of BDDrFVIII in the patient population. Investigators predicted and recorded estimates of intra-operative blood loss and intra-operative transfusion needs preoperatively based on the assumption that surgery would be completed without major complications; blood loss was rated as ‘normal’ or ‘abnormal’. Information about infusions of study drug, bleeding episodes (categorized as spontaneous or traumatic; expected surgical blood loss was not included in characterizing bleeding episodes), blood loss and transfusions was recorded intra-operatively and throughout the trial in medical records and patient diaries.

The incidence of less-than-expected therapeutic effect (LETE) was also evaluated in the prophylactic, on-demand and low recovery settings. Definitions of LETE in these specific circumstances have been previously described [2]. Assessment of FVIII:C for preoperative planning and to monitor intra-operative and postoperative dosing was performed using assays for FVIII:C activity performed at the local institution. Specimens for central laboratory measurements of FVIII:C, using the one-stage clotting assay, were collected in parallel, analysed and used for analysis of PK parameters. For BI patients, the FVIII recovery study was performed with blood samples for FVIII activity taken within 2 h before and 15 min, 30 min and 1 h after infusion of a dose of approximately 50 IU kg⁻¹ of BDDrFVIII. For CI patients, PK parameters were calculated to determine FVIII recovery and clearance via blood samples drawn within 2 h before and 15 min, 30 min, and 1, 3, 6, 9, 24, 28, 32 and 48 h after infusion of a dose of approximately 50 IU kg⁻¹ of BDDrFVIII.

Safety evaluations included recording of adverse events (AEs) [AEs and haemophilia events (AEs uniquely related to the condition of haemophilia or the direct consequence of a bleeding episode)] and concomitant treatments, physical examinations with measurements of vital signs and laboratory evaluations. Immunogenicity testing was performed by a central laboratory (Covance Laboratories, Chantilly, VA, USA) on samples obtained at screening, baseline,
day of surgery and final postoperative visits. Assessment of the presence of activity-neutralizing antibodies against FVIII (inhibitors) was performed using the Nijmegen modification of the Bethesda inhibitor assay and a normal plasma test base and reported in Bethesda Units (BU); a patient was considered to have developed a positive FVIII inhibitor if he had a titre of \( \geq 0.6 \) BU mL\(^{-1} \) in a sample assayed at the central laboratory using the Nijmegen assay after receiving study drug. Specimens testing positive for inhibitor by Nijmegen assay were then tested by Bethesda assay against a plasma-derived FVIII test base and against a BDDrFVIII test base. Serum samples were also tested for the development of antibodies to BDDrFVIII, TN8.2, the affinity ligand used in purification of BDDrFVIII and CHO cell proteins derived from the cell line used in the manufacture of BDDrFVIII, using a validated enzyme-linked immunosorbent assay (ELISA).

**Statistical analysis**

All safety analyses were performed on the intent-to-treat (ITT) population, which included all enrolled patients who received \( \geq 1 \) dose of study drug. The efficacy evaluatable population, which was used for analyses of the primary and secondary efficacy endpoints, was the subset of ITT patients that met eligibility criteria, had a major surgical procedure, had study drug administered over a period of \( \geq 26 \) days after surgery, had an efficacy assessment of study drug use in support of surgery and did not have a major protocol violation. Efficacy data on and subsequent to the date of inhibitor development were not included in efficacy analyses.

All efficacy and safety endpoints were summarized with descriptive statistics as appropriate. For continuous variables, number, mean, standard deviation (SD), median, minimum and maximum were provided. For categorical variables, frequency and percentage are presented for each category. Missing data were not imputed. The sample size was based on clinical rather than statistical considerations and is consistent with a sample size suggested by regulatory authorities.

**Results**

**Patients**

Thirty patients enrolled (22 BI, 8 CI) were treated with \( \geq 1 \) dose of BDDrFVIII and were included in the ITT population. A total of 29 patients underwent surgery and completed the study; the remaining patient withdrew for personal reasons before surgery but had baseline PK determinations. Twenty-five patients met the criteria for inclusion in the efficacy evaluable population. Reasons for exclusion from this population were inhibitor development before surgery in one patient, protocol violations in three patients (administration of autologous fresh frozen plasma during the surgical procedure) and termination from the study prior to surgery in one patient.

Median patient age was 34.5 years (range, 18–53). Demographical and baseline illness characteristics were generally similar between treatment groups, except for a greater proportional representation of severe disease (FVIII:C \( \leq 1\% \)) in the BI patient population (Table 2).

Most surgical procedures were orthopaedic; for the efficacy evaluatable population, the most common was the total joint replacements in 12 (48%) patients (11 total knee replacements and one hip replacement) and knee/elbow synovectomies in five (20%) patients.

**Concomitant treatment**

During the study, 29 of 30 (96.7%) patients used concomitant medications; most were those commonly used in the surgical setting. Non-study drug FVIII concentrates were used by 14 patients (46.7%). This largely reflects FVIII replacement therapy during the screening period and subsequent to the final visit, when patients used commercial

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<thead>
<tr>
<th>Table 2. Baseline demographics and clinical characteristics, all patients.</th>
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<tr>
<td>Age, mean years</td>
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<td>Male, ( n ) (%)</td>
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<td>White race, ( n ) (%)</td>
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<td>Weight, mean kg</td>
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<td>Previous exposure days ( \geq 150 ), ( n ) (%)</td>
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<td>Haemophilia severity, ( n ) (%)</td>
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<td>( &gt;1% ) to ( \leq 2% )</td>
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<td>Target joints, ( n ) (%)</td>
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<td>No</td>
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<td>Yes</td>
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<td>HIV status, ( n ) (%)</td>
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<td>Negative</td>
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<td>HCV status, ( n ) (%)</td>
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<td>Negative</td>
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<td>Reactive</td>
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HIV, human immunodeficiency virus; HCV, hepatitis C virus.
FVIII concentrate of their choice. At variance with protocol-specified procedures, one patient administered on-demand infusions of commercially available rFVIII on two occasions during the final postoperative period, once for the treatment of a haemorrhage, and once for physiotherapy. Antifibrinolytics were used by two patients (aminocaproic acid for 4 days and cyclokapron for 1 day; \( n = 1 \) patient each). Pharmacotherapy for systemic thromboprophylaxis was not administered to study patients. Heparin flush was used for two BI patients at one study site (surgical procedures: arthroscopic synovectomy of the elbow) to establish and maintain patency of peripherally inserted central catheter lines.

**FVIII consumption**

Extent of exposure to BDDrFVIII for the ITT population is described in Table 3. Among the ITT patients, the median total dose was 83 002 IU (range 36 500–231 044 IU) for the BI patients and 74 311 IU (range 4405–96 251 IU) for the CI patients. BI patients received a median dose of 25.5 IU kg\(^{-1}\) (range 8.4–72.9 IU kg\(^{-1}\)) per infusion over a median of 43 (range 16–72) infusions. CI patients received a mean ± SD rate of 3.7 ± 0.9 IU kg\(^{-1}\) h\(^{-1}\) during the intra-operative period and 2.8 ± 0.9 IU kg\(^{-1}\) h\(^{-1}\) in the initial postoperative period. In addition, during the final postoperative period, all CI patients received a median BI dose of 13 IU kg\(^{-1}\) (range 5.6–47.2 IU kg\(^{-1}\)) over a median of 17 (range 13–29) infusions. Exposure data were similar for the 25 patients who were evaluable for efficacy; the median total dose was 90 841 IU (range 36 500–231 044 IU) for the BI patients and 68 621 IU (range 50 854–96 251 IU) for the CI patients. Owing to the non-random designation of patients to respective treatment groups and the limited patient numbers in the CI group, no formal comparison of consumption is possible.

Two BI patients had a supplemental intra-operative dose of BDDrFVIII prompted by local laboratory FVIII:C measurements below the predetermined target FVIII:C level. For each CI patient, the initial rate of CI was informed by the respective study site standard of care rather than the clearance calculated from the patient’s baseline PK assessment. All CI of BDDrFVIII were administered by large volume preparation, for six patients (all at one study site) using normal saline and for one patient (at another study site) using 5% dextrose in water (D5W) for BDDrFVIII resuspension. For each CI patient, there was at least one occasion in which the infusion concentration of BDDrFVIII was lower than the protocol-specified limit (10 IU mL\(^{-1}\)). For five CI patients (all administered normal saline solution), the infusion rate was less than the protocol-specified limit (20 mL h\(^{-1}\)) on at least one occasion.

**Efficacy**

Target FVIII:C levels in support of the surgical procedure ranged from 1.0 to 1.5 IU mL\(^{-1}\), reflecting the varying local treatment practices of the respective study sites. The median presurgical BDDrFVIII dose was 50.6 IU kg\(^{-1}\) (range: 22.9–77.7 IU kg\(^{-1}\)). The resultant median postinfusion FVIII:C was 0.97 IU mL\(^{-1}\) (range: 0.592–1.574 IU mL\(^{-1}\)), with five of 25 patients having preinfusion FVIII:C values of ≥0.03 IU mL\(^{-1}\). These data are consistent with the results predicted by the baseline K-values.

All haemostatic efficacy ratings were reported as excellent or good during the intra-operative period, and similar results were reported for efficacy ratings at the end of the initial postoperative period (Fig. 1). The percentage of evaluable (BI and CI combined) patients with a rating of excellent was 72% in the intra-operative period and 92% at day 7/day of discharge.

Intra-operative blood loss was reported in 24 of the 25 efficacy evaluable patients; for all patients, blood loss was rated as normal (Fig. 2). In 20 of 25 patients, intra-operative blood loss was less than or equal to the volume predicted preoperatively. Thirteen patients had postoperative blood loss; in 10 cases, the blood loss was rated as normal. Of those
rated as abnormal, one followed surgical trauma to the epigastric artery, one was because of an 800 mL blood loss after hip replacement surgery and one occurred after an elbow synovectomy in which the lost blood was absorbed into the surgical dressing and could not be quantified by the investigator.

Of the nine patients predicted to require red blood cell (RBC) transfusions during the intra-operative period, only one received a transfusion. Two patients predicted not to require intra-operative RBC transfusion received transfusions with packed RBCs; for both, blood loss was reported as normal. During the postoperative period, three patients received RBC transfusions, including the patient who had surgical trauma to the epigastric artery, and one patient received fresh frozen plasma.

A total of 10 bleeding episodes in seven patients were reported in the postoperative setting and required on-demand treatment with BDDrFVIII. The range of infusion doses was 12.2–49.9 IU kg\(^{-1}\) with a median dose among CI patients of 24.4 IU kg\(^{-1}\) and a median dose among CI patients of 19.7 IU kg\(^{-1}\). Seven cases were due to injury, in three instances affecting the joint that had undergone surgery, and three cases were spontaneous. Nine episodes were treated and resolved with a single infusion of study drug, and one bleeding episode of traumatic origin required a second infusion. All but one of these episodes occurred during the final outpatient postoperative period. Response ratings to the initial BDDrFVIII infusion to treat the episode were excellent or good for all haemorrhages.

There were two true events of LETE (i.e., in the absence of confounding factors), both in the prophylactic setting with spontaneous bleeding within 48 h of a prophylactic dose of BDDrFVIII. In one patient, the investigator reported at the final postoperative visit that there had been a spontaneous soft

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**Fig. 1.** Surgical haemostasis efficacy ratings, efficacy evaluable population.

**Fig. 2.** Blood loss, efficacy evaluable population. All blood loss rated as normal unless otherwise indicated. *Postoperative blood loss rated abnormal but volume could not be quantified. **Occurred during the intraoperative period. †Postoperative blood loss rated abnormal due to hemorrhage following surgical trauma to epigastric artery. ‡Postoperative blood loss rated abnormal.
tissue bleeding episode 33.9 h after a prophylactic infusion of BDDrFVIII. The second patient had a spontaneous bleeding episode of the right hip 1 day after total knee replacement while receiving treatment by CI. Steady-state FVIII:C was 100% and 104% by the local and central laboratories respectively. The bleeding episode was not treated with any BI of study drug. The patient required no additional transfusions. Haemostatic efficacy assessment at the conclusion of the initial postoperative period had been reported as excellent.

**Pharmacokinetics**

PK data were available for all 30 patients. For both BI and CI patients, the mean ± SD K-value was 2.11 ± 0.43 IU dL$^{-1}$ per IU kg$^{-1}$, and the mean ± SD in vivo recovery value was 101 ± 20%. For CI patients undergoing full PK assessments, the mean plasma FVIII:C-vs.-time profiles increased sharply after intravenous infusion of BDDrFVIII. After the end of the infusion, the decline of FVIII:C exhibited biphasic disposition characteristics with relatively rapid but limited distribution into an extravascular space followed by a slow elimination phase with a mean ± SD t½ of 16.7 ± 5.4 h.

**Safety**

**Adverse events.** There were no reported AEs of allergic reaction or thrombosis. AEs occurring in >10% (>3 patients) of the study population were fever in 13 (43.3%), local reaction to procedure (postoperative pain in the operative wound) in 11 (36.7%), anaemia in nine (30%), infection in five (16.7%) and headache and nausea in four patients each (13.3%). AEs considered to be related to BDDrFVIII were one event of haemorrhage and one event of a false-positive inhibitor, both in the same patient, and one event of FVIII inhibitor development in a second patient. Both events were reported by the respective investigators as FVIII inhibition. Seven serious AEs (fever, postoperative haemorrhage, accidental injury, cough increased, cellulitis and both events of FVIII inhibition) were reported in five patients. All except FVIII inhibition were considered unrelated to BDDrFVIII and resolved. The two reported instances of FVIII inhibition are discussed below. There were no changes in laboratory values that were considered to be related to BDDrFVIII. Unexpected bleeding in the postoperative period was reported as an AE for two patients. Both events (abnormal bleeding following surgical trauma to the epigastric artery and unquantifiable blood loss into the surgical dressing after an arthroscopic synovectomy of the elbow) were discussed above.

**Immunogenicity.** Positive inhibitor results by Nijmegen assay were reported (by the central laboratory) for two patients, one of which had a true inhibitor under complex clinical circumstances and the other a false positive without clinical sequelae. The true inhibitor was detected in a patient who tested negative for inhibitors at screening and baseline, but subsequently had a low-titre inhibitor (0.9 BU mL$^{-1}$) detected preoperatively by the central laboratory. Prior to inhibitor onset, he had one dose of BDDrFVIII for the PK study dose at the time of his baseline assessment. Between the baseline assessment and the time of his surgery when the initial positive preoperative inhibitor was detected, the patient had 3 days of treatment with commercially available plasma-derived FVIII to successfully control a haemorrhage. As central laboratory results of the preoperative blood draw were not available until after surgery, the patient underwent a surgical knee synovectomy as planned. The patient was administered BDDrFVIII by BI for a total consumption of 66 920 IU. The patient’s preinhibitor baseline K-value was 1.96 IU dL$^{-1}$ per IU kg$^{-1}$. Postinhibitor (prior to surgery), the patient’s K-value was 1.25 IU dL$^{-1}$ per IU kg$^{-1}$. Efficacy ratings were excellent at end of surgery and at postoperative day 7/day of discharge, blood loss was rated normal and the patient had no transfusion or bleeding episode. At the final postoperative visit, the FVIII inhibitor titre was 1.51 BU mL$^{-1}$ as determined by the central laboratory, and 1 BU mL$^{-1}$ at final contact as determined by the local laboratory.

The second patient had a false-positive low-titre result (by central laboratory Nijmegen assay) at the final study visit. This low-titre FVIII inhibitor of 0.63 BU mL$^{-1}$ was reported by the central laboratory (Nijmegen result), while the same specimen tested negative in the central laboratory against plasma-derived FVIII test base and against BDDrFVIII test base, indicating that the positive Nijmegen assay result was spurious. In addition, the paired local laboratory FVIII inhibitor result from this visit was also negative. At 2-month follow-up, the local laboratory reported a titre of 0.47 BU mL$^{-1}$ (defined as a negative result) and the central laboratory reported a titre of 0.0 BU mL$^{-1}$. The ELISA result from the final visit, when the isolated spurious low-titre inhibitor was noted, was negative for an immune response to BDDrFVIII, confirming the false-positive designation of this result.
One patient developed anti-BDDrFVIII antibodies that were considered a positive immune response by ELISA at the final postoperative visit; there was no inhibitor development reported in this patient. One patient developed anti-CHO antibodies that were considered a positive immune response by ELISA at the final postoperative visit, with no reported associated allergic reaction. One patient had anti-TN8.2 antibodies at study entry but did not have an immune response following treatment with BDDrFVIII. These findings in the absence of symptoms or other evidence of FVIII neutralizing antibodies are of unknown clinical significance.

Discussion

In this prospective clinical trial of patients undergoing elective major surgery, BDDrFVIII given by either BI or CI resulted in excellent haemostasis in most patients and good haemostasis in the remainder. Blood loss was rated as normal during the intraoperative period in all patients, and in the postoperative period, abnormal bleeding was rare. Few patients required transfusions either intra-operatively or postoperatively. Median total BDDrFVIII consumption per patient (by ITT analysis) was 83,002 IU for BI and 74,311 IU for CI. BDDrFVIII was safe and well-tolerated, with a persistent low-titre inhibitor detected in one patient and a transient false-positive inhibitor detected in another patient. The central laboratory mean ± SD K-value of BDDrFVIII (2.11 ± 0.43 IU dL⁻¹ per IU kg⁻¹) aligned with prior experience (2.35 ± 0.47 IU dL⁻¹ per IU kg⁻¹) [2].

Findings in this study expand the published evidence that BDDrFVIII is safe and effective in the management of patients with haemophilia. Results from this study are consistent with published experience using the predecessor BDDrFVIII ReFacto product. In a prospective, multinational study of 38 previously treated or untreated patients undergoing 48 major or minor surgical procedures, patients were treated preoperatively with ReFacto to attain a target level of 0.5–1.0 IU mL⁻¹ for major and 0.2–0.5 IU mL⁻¹ for minor surgery [10]. During the peri-operative period, the mean dose per surgical procedure was 62 IU kg⁻¹, and a total of 1759 infusions were given over a median period of 20 days. Surgical procedures were major in 31 cases. Haemostasis was rated excellent or good by the surgeon for 99.6% of infusions given either intraoperatively or postoperatively. Blood loss and transfusion requirements were not greater than would be expected for patients without haemophilia.

In a retrospective study of 16 patients with haemophilia who had major surgical procedures and were treated with ReFacto, all patients were treated with preoperative BI followed by CI for a period of 5–21 days [11]. Intra-operative haemostasis was rated excellent or good in 12 (75%) of patients, and moderate in the remainder; there was no evidence of insufficient FVIII levels in patients with moderate ratings. Intra-operative blood loss was considered normal. Transfusions were required for bleeding episodes in 20% of patients. Reasons for the increased transfusion frequency and a greater proportion of moderate ratings in that report of treatment with predecessor product are unclear.

Administration of BDDrFVIII by BI is most commonly used to manage haemophilia patients undergoing surgical procedures and is considered the standard of care. However, adjusted-dose CI has been proposed to offer advantages over BI by preventing both wasteful high FVIII peaks and sub-therapeutic FVIII concentrations [3–8]. Data from non-randomized studies suggest a lower incidence of decreases in haemoglobin and fewer transfusions in patients treated by CI [3]. BDDrFVIII has been demonstrated to be stable in vitro in simulated CI conditions [9]. This study provides initial, albeit limited, data regarding administration of BDDrFVIII by CI. Although BDDrFVIII was successfully administered by CI in large volume preparations, the requisite 20 mL h⁻¹ minimum infusion rate when resuspended in normal saline was not easily maintained; however, this had no apparent impact on clinical efficacy outcomes. Preparing BDDrFVIII for CI in D₂W permits a minimum flow rate of 6 mL h⁻¹ without excessive adsorption loss to tubing surfaces [9] and therefore provides greater flexibility. Although efficacy results were encouraging, additional experience would be required to support any definitive conclusions regarding administration by CI.

A high incidence of thromboembolic disease is known to be associated with knee and hip joint replacement surgery in non-haemophilic patients [12, 13]. Despite the high proportion of joint replacement procedures in this study and the absence of pharmacological/systemic thromboprophylaxis, no instances of symptomatic thrombosis were observed. Potential explanations include the use of non-pharmacological/mechanical measures in a subset of patients (e.g., antiembolic stockings) and a younger patient population than might usually experience replacement surgery. An incidence of transfusions in joint replacement surgery as high as 67% has been reported in general patient populations [14]. In the current study, 4 of 12 (33%) patients who under-
went joint replacement surgery required transfusions in the intra-operative or postoperative period; providing additional evidence for the clinical efficacy of FVIII replacement with BDDrFVIII in the surgical setting.

The development of FVIII inhibitors is a serious complication of treatment with FVIII. Treatment-related risk factors for inhibitor development include surgery and a period of intensive treatment, which are hypothesized to increase risk by creating an inflammatory state [15–17]. It has been suggested that treatment using CI may increase this risk [18]. In the current study, one patient treated by BI developed a low-titre inhibitor after exposure to a single dose of study drug preoperatively followed by his usual replacement therapy over 3 days; the low-titre inhibitor was present at final follow-up in this patient. In a second patient treated by BI, a transient false-positive inhibitor was reported at the final study visit.

In conclusion, the findings of this study provide additional evidence that BDDrFVIII is efficacious for surgical prophylaxis in haemophilia A patients undergoing major surgery when administered either by intravenous bolus or CI. BDDrFVIII is associated with a favourable safety profile and low frequency of immune response.

Acknowledgements

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Disclosures

L. Rusen has acted as a speaker for Wyeth Romania and have received a small fee for this contribution. R. Gruppo has acted as a paid consultant and as a medical advisory board member to Wyeth Pharmaceuticals. A. C O’Brien, P. Kelly, D. Roth and S. Arkin are employees of Pfizer Inc.

References

INDICATIONS AND USAGE

XYNTHA (antihemophilic factor (recombinant)) is indicated in adults and children with hemophilia A for control and prevention of bleeding episodes and for perioperative management.

• Initiate treatment with XYNTHA under the supervision of a physician experienced in the treatment of hemophilia A.

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

Dosage and Administration

1. Dosing

• The required dose is determined using the following formula:

  Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL), where IU = International Unit.

• Frequency of XYNTHA administration is determined by the type of bleeding episode and the recommendation of the treating physician.

2. Preparation and Reconstitution

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

3. Use of a XYNTHA Vial Kit and a XYNTHA SOLOFUSE™ Kit

4. Administration

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

5. Monitoring Laboratory Tests

   • Frequency of factor VIII activity testing is determined by the type of bleeding episode and the recommendation of the treating physician.

6. Clinical Trials Experience

   • Headache, arthralgia, pyrexia, and cough have been reported.

7. Immunogenicity

   • Anaphylaxis and severe hypersensitivity reactions are possible. Patients may develop hypersensitivity to hamster protein, which is present in trace amounts in XYNTHA. Should such reactions occur, discontinue treatment with the product and administer appropriate treatment.

8. Economic Issues

   • The most common adverse reactions (%) with XYNTHA in adult and pediatric PTPs were headache, arthralgia, pyrexia, and cough.

9. Use in Specific Populations

   • Pregnancy: No or animal data. Use only if clearly needed.
   • Pediatrics: Half-lives are shorter, volumes of distribution are larger, and recovery is lower after XYNTHA administration in children. Higher or more frequent dosing may be needed.

10. Hemostasis

   • The required dose is determined using the following formula:

     Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL), where IU = International Unit.

11. Nursing Mothers

   • Breastfeeding is not a contraindication to the use of XYNTHA in women who are breastfeeding.

12. Labor and Delivery

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

13. Animal Toxicology and/or Pharmacology

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

14. Clinical Studies

   • Clinical Trials Experience

15. References

16. How Supplied/Storage and Handling

17. Patient Counseling Information

*Sections or subsections omitted from the full prescribing information are not listed in this document.

Control and Prevention of Bleeding Episodes

A guide for dosing XYNTHA for the control and prevention 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 Control and Prevention of Bleeding Episodes

<table>
<thead>
<tr>
<th>Type of Bleeding Episode</th>
<th>Factor VIII Level Required (IU/dL or % of normal)</th>
<th>Frequency of Doses (hours)</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>20–40</td>
<td>12-24</td>
<td>At least 1 day, depending upon the severity of the bleeding episode.</td>
</tr>
<tr>
<td>Moderate</td>
<td>30–60</td>
<td>12-24</td>
<td>3-4 days or until adequate local hemostasis is achieved.</td>
</tr>
<tr>
<td>Major</td>
<td>60–100</td>
<td>8-24</td>
<td>Until bleeding is resolved.</td>
</tr>
</tbody>
</table>

Perioperative Management

A guide for dosing XYNTHA during surgery (perioperative management) is provided in Table 2. Maintain the plasma factor VIII activity 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.

Full Prescribing Information: Contents

1. INDICATIONS AND USAGE

2. DOSAGE AND ADMINISTRATION

3. DOSAGE FORMS AND STRENGTHS

4. CONTRAINDICATIONS

5. WARNINGS AND PRECAUTIONS

6. ADVERSE REACTIONS

7. CLINICAL PHARMACOLOGY

8. USE IN SPECIFIC POPULATIONS

9. DESCRIPTION

10. REFERENCES

11. HOW SUPPLIED/STORAGE AND HANDLING

12. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

7. Break off the tamper-resistant plastic tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted XYNTHA immediately), so place the cap on its top on a clean surface in a spot where it would be least likely to become environmentally contaminated.

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

9. Place the XYNTHA vial, with the adapter attached, on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.

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

11. Without removing the syringe, gently swirl the contents of the XYNTHA vial until the powder is dissolved.

Note: The final solution should be inspected visually for particulate matter before administration. The solution should be clear to slightly opalescent and colorless. If it is not, discard the solution and use a new kit.

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

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

Note: If the solution is not used immediately, carefully replace the syringe cap. Do not touch the syringe tip or the inside of the cap.

Store the reconstituted solution at room temperature prior to administration, but use within 3 hours after reconstitution.

XYNTHA, when reconstituted, contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of XYNTHA, including storage time elapsed in a PVC container following reconstitution. The tubing of the infusion set included with this kit does not contain DEHP.

2.3 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.

<table>
<thead>
<tr>
<th>Table 2: Dosing for Perioperative Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Surgery</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Minor</td>
</tr>
<tr>
<td>Major</td>
</tr>
</tbody>
</table>

2.2 Preparation and Reconstitution

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

Note:
- If the patient uses more than one vial of XYNTHA per infusion, reconstitute each vial according to the following instructions. Remove the diluent syringe, leaving the vial adapter in place. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of each vial. Do not detach the diluent syringe or the large luer lock syringe until ready to attach the large luer lock syringe to the next vial adapter.
- If the patient uses one vial of XYNTHA with one XYNTHA SOLOFUSE™ for the infusion, reconstitute the vial and the syringe according to the instructions for each respective product kit. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of the vial and the syringe. See Dosage and Administration (2.4).

Reconstitution
1. Allow the XYNTHA vial and the prefilled diluent syringe to reach room temperature.
2. Remove the plastic flip-top cap from the XYNTHA vial to expose the central portions of the rubber stopper.
3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any surface.
4. Peel back the cover from the clear plastic vial adapter package. Do not remove the adapter from the package.
5. Place the XYNTHA vial on a flat surface. While holding the adapter package, place the vial adapter over the XYNTHA vial and press down firmly on the package until the adapter spike penetrates the vial stopper.
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

7. Break off the tamper-resistant plastic tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted XYNTHA immediately), so place the cap on its top on a clean surface in a spot where it would be least likely to become environmentally contaminated.

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

9. Place the XYNTHA vial, with the adapter attached, on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.

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

11. Without removing the syringe, gently swirl the contents of the XYNTHA vial until the powder is dissolved. Note: The final solution should be inspected visually for particulate matter before administration. The solution should be clear to slightly opalescent and colorless. If it is not, discard the solution and use a new kit.

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

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

Note: If the solution is not used immediately, carefully replace the syringe cap. Do not touch the syringe tip or the inside of the cap.

Store the reconstituted solution at room temperature prior to administration, but use within 3 hours after reconstitution.

XYNTHA, when reconstituted, contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of XYNTHA, including storage time elapsed in a PVC container following reconstitution. The tubing of the infusion set included with this kit does not contain DEHP.

2.3 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.

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

1. Reconstitute the XYNTHA vial using the instructions described in Preparation and Reconstitution [see Dosage and Administration (2.2)].
2. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the vial and the vial adapter in place.

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

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

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

6. Detach and discard the empty XYNTHA SOLOFUSE™ from the vial adapter. 
   Note: If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.

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

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

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

10. Attach the infusion set to the large luer lock syringe as directed [see Dosage and Administration (2.3)].

3 DOSAGE FORMS AND STRENGTHS
XYNTHA is available as a white to off-white lyophilized powder in the following nominal dosages:
- 250 International Units
- 500 International Units
- 1000 International Units
- 2000 International Units

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. XYNTHA was evaluated in five clinical studies (N=155), four completed studies with adult and pediatric PTPs and one ongoing study in pediatric PTPs < 6 years of age. 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 previously treated patients (PTPs) with hemophilia A (factor VIII activity in plasma [FVIII:C] ≤ 2%) who received XYNTHA for routine prophylaxis and on-demand treatment. Ninety-four subjects received at least one dose of XYNTHA, resulting in a total of 6,775 infusions [see Clinical Studies (14)]. The second study (n=30) examined the use of XYNTHA for surgical prophylaxis in previously treated patients with severe or 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 1161 infusions. One subject received XYNTHA for a pre-surgery pharmacokinetic assessment only and did not undergo surgery. [see Clinical Studies (14)]

Across all studies, safety was evaluated in 48 previously treated pediatric patients <16 years of age (28 children, <6 years of age and 20 adolescents, 12 to <16 years of age). A total of 7,150 infusions of XYNTHA were administered with a median dose per infusion of 29 IU/kg (min, max: 9.108 IU/kg). Across all studies, the most common adverse reactions (≥10%) with XYNTHA in adult and pediatric PTPs were headache (26% of subjects), arthralgia (25%), pyrexia (21%), cough (11%). Other adverse reactions reported in ≥5% of subjects were: diarrhea (8%), vomiting (7%), asthenia (7%), and nausea (6%).

6.2 Immunogenicity

There is a potential for immunogenicity with therapeutic proteins. The development of factor VIII inhibitors with XYNTHA was evaluated in 144 adult and pediatric PTPs with at least 50 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, 3 subjects developed factor VIII inhibitors (2.1%).

The clinical studies for XYNTHA examined 124 subjects (94 for bleeding and 30 for surgery) who had previously been treated with factor VIII (PTPs). In the safety and efficacy study, two subjects with inhibitors were observed in 89 subjects (2.2%) who completed ≥50 exposure days. In a Bayesian statistical analysis, results from this study were used to update PTP results from a prior supporting study using XYNTHA manufactured at the initial facility (with one de novo and two recurrent inhibitors observed in 110 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, safety was evaluated in 40 previously treated pediatric patients <16 years of age with at least 50 EDs (25 children, <6 years of age and 15 adolescents, 12 to <16 years of age). Of these, one pediatric subject developed an inhibitor.

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

6.3 Postmarketing Experience

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

The following postmarketing adverse reactions have been reported for XYNTHA: Anaphylaxis

Inadequate therapeutic response

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

In the completed open label safety and efficacy study of XYNTHA (n=94), 17 adolescent subjects 12 to <16 years of age with severe or moderately severe hemophilia A (FVIII:C ≤ 2%), who were previously treated with at least 150 EDs to FVIII products, received XYNTHA for on-demand and follow-up treatment. The median dose per infusion was 47 IU/kg (min-max: 24-74) and the median exposure per subject was 6 days (min-max: 1-26). Of the 17 subjects <16 yrs of age who received at least 1 dose of XYNTHA, 10 subjects had bleeding episodes during the study. Among the 10 subjects with response assessments, a total of 66 bleeding episodes were treated with on-demand infusions of XYNTHA. The majority of the bleeding episodes (63/66 or 95.5%) resolved with 1 or 2 infusions. Thirty-eight (38) of 66 bleeding episodes (57.6%) were rated excellent or good in their response to initial treatment, 24 (36.4%) were rated as moderate and 4 (6.1%) were not rated.

Additional data are available from a safety and efficacy study of XYNTHA in children <6 years of age with moderately severe or severe hemophilia A (FVIII:C ≤ 2%) and with at least 20 prior EDs to FVIII products. In this study subjects received XYNTHA for on-demand and follow-up treatment of bleeding episodes. The median dose per infusion was 28 IU/kg and the median exposure per subject was 16 days. Of the 27 subjects <6 years of age who received at least 1 dose of XYNTHA, 25 had bleeding episodes during the study. Among the 24 subjects with response assessments there were 493 bleeds. The majority of the bleeding episodes (482/493 or 93.7%) resolved with 1 or 2 infusions. Subjects rated the outcomes of infusions on a four-point scale: 1=excellent, 2=good, 3=moderate, and 4=poor. Of 493 bleeding episodes treated with XYNTHA, 468 (94.9%) were rated excellent or good in their response to initial treatment and 22 (4.5%) were rated as moderate.

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 Clinical Pharmacology (12.3)]

8.5 Geriatric Use

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

11 DESCRIPTION

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

The rAHF in XYNTHA is a purified glycoprotein, with an approximate molecular mass of 170 kDa consisting of 1,438 amino acids, which does not contain the B-domain.10 The amino acid sequence of the rAHF is comparable to the 90 + 80 kDa form of human coagulation factor VIII.

The purification process uses a series of chromatography steps, one of which is based on affinity chromatography using a patented synthetic peptide affinity ligand.11 The process also includes a solvent-detergent viral inactivation step and a virus-retaining nanofiltration step.

The potency expressed in International Units (IU) is determined using the chromogenic assay of the European Pharmacopoeia. The Wyeth manufacturing reference standard for potency has been calibrated against the World Health Organization (WHO) International Standard for factor VIII activity using the one-stage clotting assay. The specific activity of XYNTHA is 5,500 to 9,900 IU per milligram of protein. XYNTHA is formulated as a sterile, nonpyrogenic, non preservative, lyophilized powder preparation for intravenous injection. Each single-use vial contains nominally 250, 500, 1000, or 2000 IU of XYNTHA. Upon reconstitution, the product is a clear to slightly opalescent, colorless solution that contains sodium chloride, sucrose, L-histidine, calcium chloride, and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

The pharmacokinetic parameters of XYNTHA in 30 previously treated adult patients (PTP) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA are summarized in Table 3.

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

In a separate study, 8 of 30 subjects at least 12 years old with hemophilia A undergoing elective major surgery received a single 50 IU/kg infusion of XYNTHA. The pharmacokinetic parameters in these subjects are also summarized in Table 3.
...bleeds or 58.2%). Forty-two bleeds (42/70 or 60%) reported to have experienced bleeding prior to switching to XYNTHA.

- The median annualized bleeding rate (ABR) for all bleeding episodes was 1.9 (mean 3.9, range 0-42.1).

- Seven of these bleeding episodes occurred in subjects prior to switching to XYNTHA.

- Of the 94 subjects enrolled in this study, 30 evaluable subjects participated in a randomized, placebo-controlled, parallel-group, double-blind trial.

- All subjects had received prior prophylaxis treatment experience with factor VIII concentrates. The median age for the 94 treated subjects was 24 years (mean 27.7 and range 12-60 years). All subjects had received prior treatment with at least one factor VIII concentrate.

- For routine prophylaxis, XYNTHA was administered at a dose of 30 ± 5 IU/kg 3 times a week for 48 weeks (to 1st Infusion) or condition worsens. No Response: No improvement after an infusion, with no additional infusion administered.

- Time of Hemostatic Efficacy Assessment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Children (n=5)</th>
<th>Adolescents (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (min - max, yr)</td>
<td>3.7 - 5.8</td>
<td>14 - 15</td>
</tr>
<tr>
<td>Cmax (IU/mL)</td>
<td>0.78 ± 0.34</td>
<td>0.97 ± 0.21</td>
</tr>
<tr>
<td>AUC∞ (IU·h/mL)</td>
<td>12.2 ± 6.50</td>
<td>8.5 ± 4.0</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>8.3 ± 2.7</td>
<td>6.9 ± 2.4</td>
</tr>
<tr>
<td>CL (mL/hr/kg)</td>
<td>6.29 ± 4.87</td>
<td>6.62 ± 2.16</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>66.9 ± 55.6</td>
<td>67.1 ± 13.6</td>
</tr>
<tr>
<td>Recovery</td>
<td>1.52 ± 0.69</td>
<td>1.95 ± 0.41</td>
</tr>
<tr>
<td>(IU/µL per IU/kg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Abbreviations: Cmax = area under the plasma concentration-time curve from zero to infinity; AUC∞ = area under the plasma concentration-time curve from zero to infinity; CL = clearance; Vss = volume of distribution at steady-state; t1/2 = plasma elimination half-life; SD = standard deviation; Vss = volume of distribution at steady-state.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with XYNTHA to assess its mutagenic or carcinogenic potential. XYNTHA has been shown to be comparable to the predecessor product with regard 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.

12.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

Safety and Efficacy Study

In an open-label safety and efficacy study (n=94), subjects received XYNTHA in a routine prophylaxis treatment regimen with on-demand treatment administered as clinically indicated. All 94 subjects were treated with at least one dose and all are included in the intent-to-treat (ITT) population. All subjects had been previously treated (previously treated patients or PTPs) with factor VIII. Eighty-nine (89) subjects accrued ≥ 50 exposure days (EDs). Median age for the 94 treated subjects was 24 years (mean 27.7 and range 12-60 years). All subjects had ≥ 150 previous exposure days with baseline FVIII activity level of ≥ 2%.

Of the 94 subjects enrolled in this study, 30 evaluable subjects participated in a randomized crossover pharmacokinetics study. Twenty-five (25/90) of these subjects with FVIII:C ≤ 1% completed both the first (PK1) and the second (PK2) pharmacokinetic assessments (see Clinical Pharmacology (12.3)).

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

Fifty-three subjects (53/94) received XYNTHA on-demand treatment for a total of 187 bleeding episodes. Seven of these bleeding episodes occurred in subjects prior to switching to a prophylaxis treatment regimen. One hundred ten of 180 bleeds (110/180 or 61.1%) occurred ≥ 48 hours after the last dose and 39.9% (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 58.2%). Forty-two bleeds (42/70 or 60%) reported to have experienced bleeding prior to switching to XYNTHA.

- The majority of bleeds occurring ≥ 48 hours after the last prophylaxis dose were traumatic (64/110 bleeds or 58.2%). Forty-two bleeds (42/70 or 60%) reported to have experienced bleeding prior to switching to XYNTHA.

- The median annualized bleeding rate (ABR) for all bleeding episodes was 1.9 (mean 3.9, range 0-42.1).

- Seven of these bleeding episodes occurred in subjects prior to switching to a prophylaxis treatment regimen. One hundred ten of 180 bleeds (110/180 or 61.1%) occurred ≥ 48 hours after the last dose and 39.9% (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 58.2%). Forty-two bleeds (42/70 or 60%) reported to have experienced bleeding prior to switching to XYNTHA.

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16 HOW SUPPLIED/STORAGE AND HANDLING

**How Supplied**

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

- 250 International Units Kit: NDC 58394-012-01
- 500 International Units Kit: NDC 58394-013-01
- 1000 International Units Kit: NDC 58394-014-01
- 2000 International Units Kit: NDC 58394-015-01

Each XYNTHA Vial Kit contains: one prefilled diluent syringe containing 4 mL 0.9% Sodium Chloride with plunger rod for assembly, one vial adapter, one sterile infusion set, two alcohol swabs, one bandage, one gauze pad, and one package insert.

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

**Storage and Handling**

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

**17 PATIENT COUNSELING INFORMATION**

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

Patient Information

XYNTHA® /ZIN-tha/
[Antihemophilic Factor (Recombinant)]

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

What is XYNTHA?
XYNTHA is an injectable medicine that is used to help control and prevent bleeding in people with hemophilia A. Hemophilia A is also called classic hemophilia. Your healthcare provider may give you XYNTHA when you have surgery.

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

What should I tell my healthcare provider before using XYNTHA?
Tell your healthcare provider about all of your medical conditions, including if you:
- have any allergies, including allergies to hamsters.
- are pregnant or planning to become pregnant. It is not known if XYNTHA may harm your unborn baby.
- are breastfeeding. It is not known if XYNTHA passes into your milk and if it can harm your baby.

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

How should I infuse XYNTHA?
Step-by-step instructions for infusing with XYNTHA are provided at the end of this leaflet.

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

Call your healthcare provider right away if bleeding is not controlled after using XYNTHA.

Your body can make antibodies against XYNTHA (called “inhibitors”) that may stop XYNTHA from working properly. Your healthcare provider may need to take blood tests from time to time to monitor for inhibitors.

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

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

What are the possible side effects of XYNTHA?
Call your healthcare provider or go to the emergency department right away if you have any of the following symptoms because these may be signs of a serious allergic reaction:
- wheezing
- difficulty breathing
- chest tightness
- turning blue (look at lips and gums)
- fast heartbeat
- swelling of the face
- faintness
- rash
- hives

Common side effects of XYNTHA are
- headache
- fever
- nausea
- vomiting
- diarrhea
- weakness

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

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

Do not freeze.

Protect from light.

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

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

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

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

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

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

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

Instructions for Use

XYNTHA® /ZIN-tha/
[Antihemophilic Factor (Recombinant)]

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

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

PREPARATION AND RECONSTITUTION OF XYNTHA®

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

Reconstitution

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

1. Let the XYNTHA vial and the prefilled diluent syringe reach room temperature.
2. Remove the plastic flip-top cap from the XYNTHA vial to show the center part of the rubber stopper.

3.  Once the vials are open, finish reconstituting XYNTHA as soon as possible. This will help to keep them germ-free.

4.  For additional instructions on the use of a XYNTHA Vial Kit and a XYNTHA SOLOFUSE™ kit, see detailed information provided after the INFUSION OF XYNTHA section.

Reconstitution

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

1. Let the XYNTHA vial and the prefilled diluent syringe reach room temperature.
2. Remove the plastic flip-top cap from the XYNTHA vial to show the center part of the rubber stopper.

3.  Once the vials are open, finish reconstituting XYNTHA as soon as possible. This will help to keep them germ-free.

4.  For additional instructions on the use of a XYNTHA Vial Kit and a XYNTHA SOLOFUSE™ kit, see detailed information provided after the INFUSION OF XYNTHA section.

Reconstitution

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

1. Let the XYNTHA vial and the prefilled diluent syringe reach room temperature.
2. Remove the plastic flip-top cap from the XYNTHA vial to show the center part of the rubber stopper.
3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.

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

5. Place the XYNTHA vial on a flat surface. While holding the adapter in the package, place the vial adapter over the XYNTHA vial. Press down firmly on the package until the adapter snaps into place on top of the vial, with the adapter spike going into the vial stopper.

6. Grasp the plunger rod as shown in the picture below. Do not touch the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

7. Break off the tamper-resistant, plastic tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if reconstituted XYNTHA is not used immediately), so place the cap on its top on a clean surface in a spot where it will stay clean.

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

9. Place the XYNTHA vial on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.

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

11. With the syringe still connected to the adapter, gently swirl the contents of the vial until the powder is dissolved. Look carefully at the final solution. The solution should be clear to slightly opalescent and colorless. If it is not, throw away the solution and use a new kit.

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

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

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

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

INFUSION OF XYNTHA

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

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

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

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

1. Attach the syringe to the luer end of the provided infusion set tubing.
2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab provided in the kit.
3. Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein as instructed by your healthcare provider. Remove the tourniquet. Verify proper needle placement.

4. Infuse the reconstituted XYNTHA product over several minutes. Your comfort level should determine the rate of infusion.

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

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

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

ADDITIONAL INSTRUCTIONS

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

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

Use of a XYNTHA Vial Kit with a XYNTHA SOLOFUSE™ Kit

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

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

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

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

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

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

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

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

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

8. Detach the large luer lock syringe from the vial adapter by gently turning and pulling the syringe counterclockwise. Throw away the empty XYNTHA vial with the adapter attached.

9. Attach the infusion set to the large luer lock syringe as directed in the INFUSION OF XYNTHA section.

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

Manufactured by

Wyeth Pharmaceuticals Inc
A subsidiary of Pfizer Inc, Philadelphia, PA 19101

License no: 3
LAB-0516-5.0
XYNTHA® SOLOFUSE™ (antihemophilic factor (recombinant)) lyophilized powder for solution in prefilled dual-chamber syringe, for intravenous injection

Indications and Usage

- XYNTHA is a recombinant antihemophilic factor indicated in adults and children with hemophilia A for control and prevention of bleeding episodes and for perioperative management. (1)
- XYNTHA is not indicated in patients with von Willebrand's disease. (1)

Dosing and Administration

For intravenous use after reconstitution only (2)

- The required dose is determined using the following formula:
  Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL), where IU = International Unit.
- Frequency of XYNTHA administration is determined by the type of bleeding episode and the recommendation of the treating physician. (2.1, 2.2)

Dose Form and Strengths

XYNTHA SOLOFUSE is available as lyophilized powder in single-use prefilled dual-chamber syringes containing nominally 250, 500, 1000, 2000, or 3000 IU. (3)

Dosage and Administration

2.1 Dosing
2.2 Preparation and Reconstitution
2.3 Administration
2.4 Use of a XYNTHA Vial Kit and a XYNTHA® SOLOFUSE™ Kit
2.5 Use of Multiple XYNTHA® SOLOFUSE™

Full Prescribing Information: Contents*

1 Indications and Usage
2 Dosing and Administration
3 Dose Forms and Strengths
5 Warnings and Precautions
6 Adverse Reactions
7 Patient Counseling Information
8 Use in Specific Populations
9 How Supplied/Storage and Handling
10 References
11 Description
12 Clinical Pharmacology
13 Nonclinical Toxicology
14 Clinical Studies
15 References
16 How Supplied/Storage and Handling
17 Patient Counseling Information

Full Prescribing Information

1 Indications and Usage

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

- Control and prevention of bleeding episodes
- Perioperative management

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

2 Dosing and Administration

For intravenous use after reconstitution only.

2.1 Dose

- Initiate treatment with XYNTHA under the supervision of a physician experienced in the treatment of hemophilia A.
- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Titrate the administered doses to the patient's clinical response.
- 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 on the empirical finding that, on average, 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by approximately 2 IU/dL.2

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

\[
\text{Dose (International Units)} = \text{body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)}
\]

or

\[
\text{IU/dL (or % normal) = Total Dose (IU)/body weight (kg) x 2 (IU/dL)/(IU/kg)}
\]

Dosage forms and strengths

XYNTHA SOLOFUSE is available as lyophilized powder in single-use prefilled dual-chamber syringes containing nominally 250, 500, 1000, 2000, or 3000 IU. (3)

Recent Major Changes

- Revised: 10/2014
2. Remove the contents of the XYNTHA® SOLOFUSE™ Kit and place on a clean surface.

1. Allow the XYNTHA SOLOFUSE Kit to reach room temperature.

• If the patient uses one vial of XYNTHA with one XYNTHA® SOLOFUSE™ for the extraction. Including tooth extraction.

3. Use all components for 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 one vial of XYNTHA with one XYNTHA® SOLOFUSE™ for the infusion, reconstitute the vial and the syringe according to the instructions for that respective product kit. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of the vial and the syringe. [See Dosage and Administration (2.4)]
- If the patient uses multiple XYNTHA SOLOFUSE syringes for the infusion, reconstitute each syringe according to the instructions below. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of each syringe. [See Dosage and Administration (2.5)]

2.2 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 for 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 one vial of XYNTHA with one XYNTHA® SOLOFUSE™ for the infusion, reconstitute the vial and the syringe according to the instructions for that respective product kit. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of the vial and the syringe. [See Dosage and Administration (2.4)]
- If the patient uses multiple XYNTHA SOLOFUSE syringes for the infusion, reconstitute each syringe according to the instructions below. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of each syringe. [See Dosage and Administration (2.5)]

Reconstitution
1. Allow the XYNTHA SOLOFUSE Kit to reach room temperature.
2. Remove the contents of the XYNTHA® SOLOFUSE™ Kit and place on a clean surface, making sure you have all the supplies you will need.
3. Grasp the plunger rod as shown in the following diagram. Avoid contact with the shaft of the plunger rod. Screw the plunger rod firmly into the opening in the finger rest of the XYNTHA® SOLOFUSE™ by pushing and turning firmly until resistance is felt (approximately 2 turns).

5. Remove the protective blue vented sterile cap from its package. While holding the XYNTHA® SOLOFUSE™ upright, remove the grey rubber tip cap and replace it with the protective blue vented cap (prevents pressure build-up). Avoid touching the open end of both the syringe and the protective blue vented cap.

6. Gently and slowly advance the plunger rod by pushing until the two stoppers inside the XYNTHA® SOLOFUSE™ meet, and all of the diluent is transferred to the chamber containing the XYNTHA powder.

Note: To prevent the escape of fluid from the tip of the syringe, the plunger rod should not be pushed with excessive force.

7. With the XYNTHA® SOLOFUSE™ remaining upright, swirl gently several times 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.

8. Holding the XYNTHA® SOLOFUSE™ in an upright position, slowly advance the plunger rod until most, but not all, of the air is removed from the drug product chamber.

2.3 Administration

For intravenous infusion after reconstitution only.
Inspect the final XYNTHA solution visually for particulate matter and discoloration prior to administration. The solution should be clear to slightly opalescent and colorless. If it is not, discard the solution and use a new kit.
Administer XYNTHA solution using the infusion set included in the kit. Do not administer reconstituted XYNTHA in the same tubing or container with other medicinal products.

1. After removing the protective blue vented cap, firmly attach the intravenous infusion set provided in the kit onto the XYNTHA® SOLOFUSE™.

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 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 XYNTHA® SOLOFUSE™, and other used medical supplies in an appropriate container.

2.4 **Use of a XYNTHA Vial Kit with a XYNTHA® SOLOFUSE™ Kit**

These instructions are for the use of only one XYNTHA vial kit with one XYNTHA® SOLOFUSE™ kit. For further information, please contact the Medical Information Department at Wyeth Pharmaceuticals, 1-800-438-1985.

1. Reconstitute the XYNTHA vial using the instructions included with the product kit.

2. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the vial and the vial adapter in place.

3. Reconstitute the XYNTHA® SOLOFUSE™ using the instructions described in Preparation and Reconstitution [see Dosage and Administration (2.2)]. Remember to remove most, but not all, of the air from the drug product chamber.

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

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

6. Detach and discard the empty XYNTHA® SOLOFUSE™ from the vial adapter.
   
   **Note:** If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.

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

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

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

10. Attach the infusion set to the large luer lock syringe as directed [see Dosage and Administration (2.3)].

2.5 **Use of Multiple XYNTHA® SOLOFUSE™ Kits**

The instructions below are for the use of multiple XYNTHA® SOLOFUSE™ kits with a 10 milliliter or larger luer lock syringe. For further information, please contact the Medical Information Department at Wyeth Pharmaceuticals, 1-800-438-1985.

**Note:** Luer-to-luer syringe connectors are not provided in these kits. Instruct patients to contact their XYNTHA supplier to order.

1. Reconstitute all XYNTHA® SOLOFUSE™ according to instructions described in Preparation and Reconstitution [see Dosage and Administration (2.2)].

2. Holding the XYNTHA® SOLOFUSE™ in an upright position, slowly advance the plunger rod until most, but not all, of the air is removed from the drug product chamber.

3. Remove the luer-to-luer syringe connector from its package.

4. After removing the protective blue vented cap, connect a sterile 10 milliliter or larger luer lock syringe to one opening (port) in the syringe connector and the XYNTHA® SOLOFUSE™ to the remaining open port on the opposite end.

5. With the XYNTHA® SOLOFUSE™ on top, slowly depress the plunger rod until the contents empty into the large luer lock syringe.

6. Remove the empty XYNTHA® SOLOFUSE™ and repeat procedures 3 and 4 above for any additional reconstituted XYNTHA SOLOFUSE.

7. Remove the luer-to-luer syringe connector from the large luer lock syringe and attach the infusion set as directed [see Dosage and Administration (2.3)].

3 **DOSE FORMS AND STRENGTHS**

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

- 250 International Units
- 500 International Units
- 1000 International Units
- 2000 International Units
- 3000 International Units

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

4 **CONTRAINDICATIONS**

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

5 **WARNINGS AND PRECAUTIONS**

5.1 **Hypersensitivity Reactions**

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

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

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

5.3 Monitoring Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. XYNTHA was evaluated in five clinical studies (N=155), four completed studies with adult and pediatric PTPs and one ongoing study in pediatric PTPs <6 years of age.

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

Across all studies, safety was evaluated in 48 previously treated pediatric patients <16 years of age (28 children, <6 years of age and 20 adolescents, 12 to <16 years of age). A total of 7,150 infusions of XYNTHA were administered with a median dose per infusion of 29 IU/kg (min, max: 9,108 IU/kg).

Across all studies, the most common adverse reactions (≥10%) with XYNTHA in adult and pediatric PTPs were headache (26% of subjects), arthralgia (25%), pyrexia (21%), cough (11%). Other adverse reactions reported in ≥5% of subjects were: diarrhea (8%), vomiting (7%), asthenia (7%), and nausea (6%).

6.2 Immunogenicity

There is a potential for immunogenicity with therapeutic proteins. The development of factor VIII inhibitors with XYNTHA was evaluated in 144 adult and pediatric PTPs with at least 50 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, 3 subjects developed factor VIII inhibitors (2.1%).

The clinical studies for XYNTHA examined 124 subjects (94 for bleeding and 30 for surgery) who had previously been treated with factor VIII (PTPs). In the safety and efficacy study, two subjects with inhibitors were observed in 89 subjects (2.2%) who completed ≥50 exposure days.

In a Bayesian statistical analysis, results from this study were used to update PTP results from a prior supporting study using XYNTHA manufactured at the initial facility (with one de novo and two recurrent inhibitors observed in 110 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-TNF.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, safety was evaluated in 40 previously treated pediatric patients <16 years of age with at least 50 EDs (25 children, <6 years of age and 15 adolescents, 12 to <16 years of age). Of these, one pediatric subject developed an inhibitor.

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

6.3 Postmarketing Experience

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

The following postmarketing adverse reactions have been reported for XYNTHA: Anaphylaxis

Inadequate therapeutic response.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

In the completed open label safety and efficacy study of XYNTHA (n=94), 17 adolescent subjects 12 to <16 years of age with severe or moderately severe hemophilia A (FVIII:C ≤2%), who were previously treated with at least 150 EDs to FVIII products, received XYNTHA for on-demand and follow-up treatment. The median dose per infusion was 47 IU/kg (min-max: 24-74) and the median exposure per subject was 6 days (min-max: 1-26).

Of the 17 subjects <16 yrs of age who received at least 1 dose of XYNTHA, 10 subjects had bleeding episodes during the study. Among the 10 subjects with response assessments, a total of 66 bleeding episodes were treated with on-demand infusions of XYNTHA. The median dose for the bleeding episodes (63/66 or 95.5%) resolved with 1 or 2 infusions. Thirty-eight (38) of 66 bleeding episodes (57.6%) were rated excellent or good in their response to initial treatment, 24 (36.4%) were rated as moderate and 4 (6.1%) were not rated.

Additional data are available from a safety and efficacy study of XYNTHA in children <6 years of age with moderately severe or severe hemophilia A (FVIII:C ≤2%) and with at least 20 prior EDs to FVIII products. In this study subjects received XYNTHA for on-demand and follow-up treatment of bleeding episodes. The median dose per infusion was 28 IU/kg and the median exposure per subject was 50 exposure days. Of the 27 subjects <6 years of age who received at least 1 dose of XYNTHA, 25 had bleeding episodes during the study. Among the 24 subjects with response assessments there were 493 bleeds. The majority of the bleeding episodes (462/493 or 93.7%) resolved with 1 or 2 infusions. Subjects rated the outcomes of infusions on a pre-specified (4) point hemostatic efficacy scale. Of 493 bleeding episodes treated with XYNTHA, 468 (94.9%) were rated excellent or good in their response to initial treatment and 24 (4.9%) were rated poor.

In comparison to the pharmacokinetic parameters reported in adults, children have shorter half-lives, larger volumes of distribution and lower recovery of factor VIII activity for a given dose of XYNTHA. Therefore, higher or more frequent doses may be required in pediatric patients.

In elderly patients, the selection for an elderly patient should be individualized.

Clinical studies of XYNTHA did not include subjects aged 65 and over.

In general, dose selection for an elderly patient should be individualized.
Xyntha temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis. Determination of aPTT is a conventional in vitro assay for biological activity of factor VIII. Treatment with XYNTHA normalizes the aPTT over the effective dosing period.

### 12.2 Pharmacokinetics

The pharmacokinetic parameters of XYNTHA in 30 previously treated adult patients (PTP) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA are summarized in Table 3.

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

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

### 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with XYNTHA to assess its mutagenic or carcinogenic potential. XYNTHA has been shown to be comparable to the predecessor product with factor VIII. Eighty-nine (89) subjects accrued ≥ 50 exposure days (EDs). Median age for the 94 treated subjects was 24 years (mean 27.7 and range 12-60 years). All subjects had ≥ 150 previous exposure days with baseline FVIII activity level of ≤ 5%.

No studies were conducted with XYNTHA to assess its mutagenic or carcinogenic potential. The toxicological profile that was similar to the toxicological profile observed with the predecessor product. Toxicity associated with XYNTHA was primarily associated with anti-FVIII neutralizing antibody generation first detectable at 15 days of repeat dosing in high (approximately 735 IU/kg/day) level-dosed, non-human primates.

### 14 CLINICAL STUDIES

#### Safety and Efficacy Study

In an open label safety and efficacy study (n=94), subjects received XYNTHA in a routine prophylaxis treatment regimen with on-demand treatment administered as clinically indicated. All 94 subjects were treated with at least one dose and all are included in the intent-to-treat (ITT) population. All subjects had been previously treated (previously treated patients or PTPs) with factor VIII. Eighty-nine (89) subjects accrued ≥ 50 exposure days (EDs). Median age for the 94 treated subjects was 24 years (range 27.7 and range 12-60 years). All subjects had ≥ 150 previous exposure days with baseline FVIII activity level of ≤ 5%.

No studies were conducted with XYNTHA to assess its mutagenic or carcinogenic potential. The toxicological profile 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.

#### Hemostasis Efficacy

The mean ± SD pharmacokinetic parameters in previously treated patients with hemophilia A after a 50 IU/kg dose are summarized in Table 3.

The pharmacokinetic parameters of XYNTHA in 30 previously treated adult patients (PTP) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA are summarized in Table 3.

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

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

### Table 3: Mean ± SD XYNTHA Pharmacokinetic Parameters in Previously Treated Patients with Hemophilia A after Single 50 IU/kg Dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial Visit (n=30)</th>
<th>Month 6 (n=25)</th>
<th>Pre-surgery (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (IU/mL)</td>
<td>1.08 ± 0.22</td>
<td>1.24 ± 0.42</td>
<td>1.08 ± 0.24</td>
</tr>
<tr>
<td>AUC∞ (IU·h/mL)</td>
<td>13.5 ± 6.5</td>
<td>15.0 ± 7.5</td>
<td>16.0 ± 5.2</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>11.2 ± 5.0</td>
<td>11.8 ± 6.2*</td>
<td>16.7 ± 5.4</td>
</tr>
<tr>
<td>CL (mL/hr/kg)</td>
<td>4.51 ± 2.23</td>
<td>4.04 ± 1.87</td>
<td>3.48 ± 1.25</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>66.1 ± 33.0</td>
<td>67.4 ± 32.6</td>
<td>69.0 ± 20.1</td>
</tr>
<tr>
<td>Recovery (IU/DL per IU/kg)</td>
<td>2.15 ± 0.44</td>
<td>2.47 ± 0.84</td>
<td>2.17 ± 0.47</td>
</tr>
</tbody>
</table>

#### Abbreviations:
- AUC: area under the plasma concentration-time curve from zero to infinity
- CL: clearance
- Cmax: peak concentration
- t1/2: elimination half-life
- Vss: volume of distribution
- SD: standard deviation

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

### Table 4: Mean ± SD XYNTHA Pharmacokinetic Parameters in Previously Treated Pediatric Patients with Hemophilia A after Single 50 IU/kg Dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Children (n=5)</th>
<th>Adolescents (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (IU/mL)</td>
<td>0.78 ± 0.34</td>
<td>0.77 ± 0.21</td>
</tr>
<tr>
<td>AUC∞ (IU·h/mL)</td>
<td>12.2 ± 6.50</td>
<td>8.5 ± 4.0</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>8.3 ± 2.7</td>
<td>6.9 ± 2.4</td>
</tr>
<tr>
<td>CL (mL/hr/kg)</td>
<td>6.20 ± 4.87</td>
<td>6.26 ± 2.1</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>66.9 ± 55.6</td>
<td>67.1 ± 13.6</td>
</tr>
<tr>
<td>Recovery (IU/DL per IU/kg)</td>
<td>1.52 ± 0.69</td>
<td>1.95 ± 0.41</td>
</tr>
</tbody>
</table>

#### Abbreviations:
- AUC∞: area under the plasma concentration-time curve from zero to infinity
- CL: clearance
- Cmax: peak concentration
- t1/2: elimination half-life
- Vss: volume of distribution
- SD: standard deviation

### Table 5: Summary of Response to Infusions to Treat New Bleeding Episode by Number of Infusions Needed for Resolution

<table>
<thead>
<tr>
<th>Number of Infusions (%)</th>
<th>Response to 1st Infusion</th>
<th>Total Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Excellent</td>
<td>42 (95.5)</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Good</td>
<td>69 (78.4)</td>
<td>16 (18.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>24 (53.3)</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td>No Response</td>
<td>0 (0.0)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Not Assessed</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>139 (74.3)</td>
<td>34 (18.2)</td>
</tr>
</tbody>
</table>

#### Abbreviations:
- Excellent: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered.
- Good: Definite pain relief and/or improvement in signs of bleeding starting within 6 hours after an infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.
- 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.
- No Response: No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens.
- Includes one infusion with commercial FVIII that occurred before routine prophylaxis began.

### Perioperative Management Study

In an open-label study (n=30) for surgical prophylaxis in subjects with hemophilia A, XYNTHA was administered to 25 efficacy-evaluable PTPs with severe or moderately severe (FVIII:C ≤ 5%) hemophilia A undergoing major surgical procedures (11 total knee replacements, 1 hip replacement, 5 synovectomies, 1 left ulnar nerve transposition release, 1 ventral hernia repair/scar revision, 1 knee arthroscopy, 1 revision and debridement of the knee after a total knee replacement, 1 hip arthroplasty revision, 1 stapes replacement, 1 after an gunshot wound, and 1 after an above knee amputation).

The results of the hemostatic efficacy ratings for these subjects are presented in Table 6.

### Table 6: Summary of Hemostatic Efficacy

<table>
<thead>
<tr>
<th>Time of Hemostatic Efficacy Assessment</th>
<th>Excellent</th>
<th>Good</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of surgery</td>
<td>16 (72%)</td>
<td>7 (28%)</td>
<td>23</td>
</tr>
<tr>
<td>End of initial postoperative period</td>
<td>23 (92%)</td>
<td>2 (8%)</td>
<td>25</td>
</tr>
</tbody>
</table>

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


16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

XYNTHA® SOLOFUSE™ is supplied in a kit that includes the XYNTHA lyophilized powder containing nominally 250, 500, 1000, 2000 or 3000 IU and 4 mL 0.9% Sodium Chloride solution for reconstitution in a prefilled dual-chamber syringe:

- 250 International Units Kit: NDC 58394-016-03
- 500 International Units Kit: NDC 58394-023-03
- 1000 International Units Kit: NDC 58394-024-03
- 2000 International Units Kit: NDC 58394-025-03
- 3000 International Units Kit: NDC 58394-016-03

Each XYNTHA® SOLOFUSE™ Kit contains: one plunger rod for assembly, one sterile 3000 International Units Kit: NDC 58394-016-03

Storage and Handling

Product as Packaged for Sale:

- Store XYNTHA® SOLOFUSE™ under refrigeration at a temperature of 2°C to 8°C (36°F to 46°F) for up to 36 months from the date of manufacture until the expiration date stated on the label.
- Within the expiration date, XYNTHA® SOLOFUSE™ also may be stored at room temperature not to exceed 25°C (77°F) for up to 3 months.
- Clearly record the starting date at room temperature storage in the space provided on the outer carton. At the end of the 3-month period, immediately use or discard the product.
- Do not put the product back into the refrigerator.
- Do not use XYNTHA® SOLOFUSE™ after the expiration date stated on the label or after 3 months when stored at room temperature, whichever is earlier.
- Do not freeze. (Freezing may damage the XYNTHA® SOLOFUSE™.)
- During storage, avoid prolonged exposure of XYNTHA® SOLOFUSE™ to light.
- Store the reconstituted solution at room temperature prior to administration. Remember to Administer XYNTHA® SOLOFUSE™ within 3 hours after reconstitution or after removal of the grey rubber tip cap from the product.

17 PATIENT COUNSELING INFORMATION

- Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise patients to report any adverse reactions or problems that concern them when taking XYNTHA to their healthcare provider.
- Allergic-type hypersensitivity reactions are possible. Discuss the early signs of hypersensitivity reactions (including hives [rash with itching], generalized urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis. Advise patients to discontinue use of the product, call their healthcare provider, and go to the emergency department if these symptoms occur.
- Advise patients to contact their healthcare provider if they experience a lack of a clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy, or if they are breastfeeding.
- Local irritation may occur when infusing XYNTHA SOLOFUSE™.
- Advise patients to consult their healthcare provider prior to travel and to bring an adequate supply of XYNTHA SOLOFUSE™, based on their current regimen, for anticipated treatment when traveling.
FDA-Approved Patient Labeling

Patient Information

XYNTHA® SOLOFUSE™ /ZIN-tha/ [Antihemophilic Factor (Recombinant)]

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

What is XYNTHA?

XYNTHA is an injectable medicine that is used to help control and prevent bleeding in people with hemophilia A. Hemophilia A is also called classic hemophilia. Your healthcare provider may give you XYNTHA when you have surgery. XYNTHA is not used to treat von Willebrand’s disease.

What should I tell my healthcare provider before using XYNTHA?

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

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

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

How should I infuse XYNTHA?

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

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

Call your healthcare provider right away if bleeding is not controlled after using XYNTHA.

Your body can make antibodies against XYNTHA (called “inhibitors”) that may stop XYNTHA from working properly. Your healthcare provider may need to take blood tests from time to time to monitor for inhibitors.

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

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

What are the possible side effects of XYNTHA?

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

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

Common side effects of XYNTHA are

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

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

How should I store XYNTHA SOLOFUSE?

Store in the refrigerator at 36° to 46°F (2° to 8°C). Do not freeze.

Protect from light.

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

Throw away any unused XYNTHA SOLOFUSE after the expiration date. Infuse within 3 hours after reconstitution or after removal of the grey rubber tip cap from the prefilled dual-chamber syringe. You can keep the reconstituted solution at room temperature before infusion for up to 3 hours. If it is not used in 3 hours, throw it away.

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

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

What else should I know about XYNTHA?

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

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

Instructions for Use

XYNTHA SOLOFUSE™ /ZIN-tha/ [Antihemophilic Factor (Recombinant)]

XYNTHA SOLOFUSE is supplied as a pre-filled dual-chamber syringe with lyophilized XYNTHA powder in one chamber and 0.9% sodium chloride solution in the other chamber. Before you can infuse it (intravenous injection), you must reconstitute the powder by mixing it with the sodium chloride solution.

Reconstitute and infuse XYNTHA SOLOFUSE™ using the infusion set provided in this kit. Please follow the directions below for the proper use of this product.

PREPARATION AND RECONSTITUTION OF XYNTHA SOLOFUSE™

Preparation

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

Reconstitution

1. Allow the XYNTHA SOLOFUSE to reach room temperature.
2. Remove the contents of the XYNTHA SOLOFUSE Kit and place on a clean surface, making sure you have all the supplies you will need.
3. Grasp the plunger rod as shown in the following diagram. Do not touch the shaft of the plunger rod. Screw the plunger rod firmly into the opening in the finger rest of the XYNTHA SOLOFUSE by pushing and turning firmly until resistance is felt (approximately 2 turns).

Throughout the reconstitution process, it is important to keep the XYNTHA SOLOFUSE upright to prevent possible leakage.
4. Holding the XYNTHA® SOLOFUSE™ upright, remove the white tamper-evident seal by bending the seal right to left (or a gentle rocking motion) to break the perforation of the cap and expose the grey rubber tip cap of the XYNTHA® SOLOFUSE™.

5. Remove the protective blue vented sterile cap from its package. While holding the XYNTHA® SOLOFUSE™ upright, remove the grey rubber tip cap and replace it with the protective blue vented cap (prevents pressure build-up). Avoid touching the open end of both the syringe and the protective blue vented cap.

6. Gently and slowly push the plunger rod until the two stoppers inside the XYNTHA® SOLOFUSE™ meet, and all of the diluent is transferred to the chamber containing the XYNTHA powder. 
   **Note:** To prevent the escape of fluid from the tip of the syringe, do not push the plunger rod with excessive force.

7. With the XYNTHA® SOLOFUSE™ remaining upright, swirl gently several times until the powder is dissolved.

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

8. Holding the XYNTHA® SOLOFUSE™ in an upright position, slowly advance the plunger rod until most, but not all, of the air is removed from the drug product chamber.

   **Note:**
   - If you are not using the solution immediately, store the syringe upright and keep the protective blue vent cap on the XYNTHA® SOLOFUSE™ until ready to infuse.
   - Infuse XYNTHA solution within 3 hours after reconstitution or removal of the grey tip cap from the XYNTHA SOLOFUSE. The reconstituted solution may be kept at room temperature for up to 3 hours prior to infusion. If you have not used it in 3 hours, throw it away.

   - If more than one XYNTHA® SOLOFUSE™ is needed for each infusion, a luer-to-luer syringe connector can be used (not included in this kit). Please contact your doctor or healthcare provider, or call the Wyeth Medical Information Department at 1-800-438-1985, for additional information.

**INFUSION OF XYNTHA**

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

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

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

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

1. After removing the protective blue vented cap, firmly attach the intravenous infusion set provided in the kit onto the XYNTHA® SOLOFUSE™.

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

3. Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein as instructed by your healthcare provider. Remove the tourniquet. Verify proper needle placement.

4. Infuse the reconstituted XYNTHA product over several minutes. Your comfort level should determine the rate of infusion.

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

   **Note:**
   - Throw away all unused solution, the empty XYNTHA® SOLOFUSE™, and other used medical supplies in an appropriate container.

   - It is a good idea to record the lot number from the XYNTHA® SOLOFUSE™ label every time you use XYNTHA. You can use the peel-off label found on the XYNTHA® SOLOFUSE™ to record the lot number.
ADDITIONAL INSTRUCTIONS

XYNTHA is also supplied in kits that include single-use vials with lyophilized powder and prefilled diluent syringes.

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

If you use multiple XYNTHA® SOLOFUSE™ kits for the infusion, reconstitute each XYNTHA® SOLOFUSE™ according to the directions above. Use a separate, 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted contents of any additional XYNTHA® SOLOFUSE™.

Use of a XYNTHA Vial Kit with a XYNTHA® SOLOFUSE™ Kit

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

1. Reconstitute the XYNTHA vial using the instructions included with the kit. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the XYNTHA vial with the vial adapter in place.

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

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

4. Slowly push the plunger rod of the XYNTHA® SOLOFUSE™ to empty the contents into the XYNTHA vial. The plunger rod may move back slightly after release.

5. Detach the empty XYNTHA® SOLOFUSE™ from the vial adapter and throw it away. If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.

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

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

8. Detach the large luer lock syringe from the vial adapter by gently turning and pulling the syringe counterclockwise. Throw away the empty XYNTHA vial with the adapter attached.

9. Attach the infusion set to the large luer lock syringe as directed in the INFUSION OF XYNTHA section.

Note: Dispose of all unused solution, the empty XYNTHA® SOLOFUSE™, and other used medical supplies in an appropriate container.

Use of Multiple XYNTHA® SOLOFUSE™ Kits

The instructions below are for the use of multiple XYNTHA® SOLOFUSE™ kits with a 10 milliliter or larger luer lock syringe. For further information, please contact your healthcare provider or call the Medical Information Department at Wyeth Pharmaceuticals, 1-800-438-1985.

Note: Luer-to-luer syringe connectors are not provided in the kits. Contact your XYNTHA supplier to order.

1. Reconstitute all XYNTHA® SOLOFUSE™ according to instructions described in PREPARATION AND RECONSTITUTION OF XYNTHA® SOLOFUSE™ section. Holding the XYNTHA® SOLOFUSE™ in an upright position, slowly push the plunger rod until most, but not all, of the air is removed from the syringe.
2. Remove the luer-to-luer syringe connector from its package.
3. After removing the protective blue vented cap, connect a sterile 10 milliliter or larger luer lock syringe to one opening (port) in the syringe connector and the XYNTHA® SOLOFUSE™ to the remaining open port on the opposite end.

4. With the XYNTHA® SOLOFUSE™ on top, slowly push the plunger rod to empty all the XYNTHA SOLOFUSE content into the large luer lock syringe.

5. Remove the empty XYNTHA® SOLOFUSE™ and repeat procedures 3 and 4 above for any additional XYNTHA® SOLOFUSE™.
6. Remove the luer-to-luer syringe connector from the large luer lock syringe and attach the infusion set as directed in the INFUSION OF XYNTHA section.

Note: Dispose of all unused solution, the empty XYNTHA® SOLOFUSE™, and other used medical supplies in an appropriate container.

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