



REVIEW ARTICLE

An improved manufacturing process for Xyntha/ReFacto AF

B. KELLEY,* M. JANKOWSKI† and J. BOOTH‡

*Process Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA; †Characterization and Analytical Development; and ‡Drug Substance Development, Wyeth BioPharma, Andover, MA, USA

Summary. ReFacto[®] Antihemophilic Factor is a second-generation antihemophilia A product manufactured using a process that includes therapeutic grade human serum albumin (HSA) in the cell culture medium, but is formulated without HSA as a stabilizer. Even though this second-generation antihemophilia product has a good safety profile, a programme was implemented to eliminate all animal- and human-derived raw materials from the production process, thus producing a third-generation product. To that end, HSA has been removed from the master and working cell banks and from the culture medium. The hybridoma-derived monoclonal antibody formerly used in the purification process has been replaced by a chemically synthesized affinity peptide, and a virus-retaining filtration step has been added to enhance the

clearance of large viruses, such as retroviruses. The purification process has been validated for the removal of a panel of model viruses and provides significant clearance of all viruses tested. Host cell- and process-derived impurity removal validations also were conducted, including host cell DNA and protein, in addition to the affinity peptide. Compared with the product manufactured according to the original process, these changes had no detectable effect on the structural integrity, stability or clinical efficacy of this antihemophilia A product. The product produced by the improved manufacturing process is named Xyntha[™]/ReFacto AF.

Keywords: factor VIII, manufacturing, ReFacto, virus removal filtration, Xyntha

Introduction

Several recombinant factor VIII (FVIII) products are approved in the United States and the European Union for the treatment of haemophilia A [1]. ReFacto[®] Antihemophilic Factor (Recombinant); Wyeth Pharmaceuticals Inc.; Philadelphia, PA, USA; 2007 is the first B-domain-deleted FVIII and was licenced in the European Union in 1998 and in the United States in 2000. It is a second-generation antihemophilia A factor product, formulated without the use of human serum albumin (HSA) as a stabilizing excipient [2]. The manufacturing process for the original ReFacto included highly purified, therapeutic-grade HSA in the cell culture medium, to support cell growth and product expression. The ReFacto purification process included an immuno-

affinity chromatography step, in which a monoclonal antibody (mAb) was used to selectively purify the FVIII molecule from a complex feedstream [2].

The elimination of animal- and human-derived raw materials from production processes precludes the introduction of adventitious agents, such as viruses, from these sources [3]. Until recently, only one recombinant FVIII product – Advate [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]; Baxter Healthcare Corporation; Westlake Village, CA, USA; 2007 – employed a manufacturing method that eliminated all human- and animal-derived raw materials from its cell-culture process. However, a mAb produced by a murine hybridoma cell line is still being used for the purification of Advate [1].

A programme was implemented to eliminate all animal- and human-derived raw materials from both the cell-culture and purification processes used to produce ReFacto, thereby fully aligning the upstream process with the albumin-free product formulation. The new process, yielding Xyntha[™] [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free] for

Correspondence: Michael Jankowski, One Burtt Rd., Andover, MA 01810, USA.

Tel.: +1 978 247 1722; fax: +1 978 247 3456;
e-mail: michael.jankowski@pfizer.com

Accepted after revision 7 November 2009

intravenous use, freeze-dried powder; Wyeth Pharmaceuticals Inc.; 2008/ReFacto AF [moroctocog alfa AF-CC], was developed with the intent to maintain product characteristics and comparability to ReFacto. This study describes the design strategy, details of production and process modifications, validation data and viral safety assessment of the improved Xyntha/ReFacto AF manufacturing process.

Original ReFacto manufacturing process

The original ReFacto manufacturing process has been described previously [2]. The cell culture process uses an inoculum train, which builds sufficient cell mass to initiate a production culture and subsequent product synthesis in a perfusion bioreactor. SP-Sepharose is used to capture and concentrate the product from the cell free conditioned medium. The product-containing SP eluate is stored frozen prior to further downstream processing. Multiple SP eluates are pooled, treated with a solvent/detergent mixture to inactivate enveloped viruses and loaded directly onto a mAb column. The product is further purified using Q-Sepharose anion exchange chromatography and Butyl-Sepharose hydrophobic interaction chromatography. Finally, size exclusion chromatography is used to exchange the product into the formulation buffer. The highly purified ReFacto is then frozen as a drug substance and tested prior to release for additional manufacturing at the fill/finish facility, to produce the lyophilized vial of ReFacto drug product that is distributed to the patient.

Rationale for and details of Xyntha/ReFacto AF process changes

The Xyntha/ReFacto AF manufacturing process was designed to leverage the knowledge and experience with the original ReFacto process by keeping the major process design elements intact (Fig. 1). This modified process closely resembles the original ReFacto manufacturing process, with specific modifications introduced to achieve the goal of eliminating all animal- and human-derived raw materials. The viral safety of the modified process is further enhanced by the introduction of a virus removal filtration (VRF) step and the replacement of the immunoaffinity purification column with a synthetic peptide ligand. The details of and rationale for these process improvements are described below.

The primary goal of the cell-bank adaptation programme was to remove HSA from the culture medium formulation and establish the new master

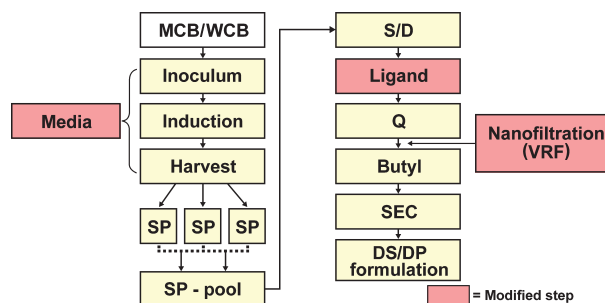


Fig. 1. The Xyntha/ReFacto AF manufacturing process. Butyl, Butyl-Sepharose; DS/DP, drug substance/drug product; MCB, master cell bank; Q, Q-Sepharose; S/D, solvent/detergent; SEC, size-exclusion chromatography; SP, SP-Sepharose; VRF, virus removal filtration; WCB, working cell bank.

cell bank (MCB) and working cell bank (WCB) lacking any human- or animal-derived raw materials. The philosophy of the cell-line adaptation programme was to leverage previous cell-line development to avoid *de novo* creation of a new production cell line, cell culture medium and cell culture process. This approach minimizes the potential to impact the cell culture process.

Comparative genotypic analysis was performed to confirm that the new MCB represents the same initial cell clone as the original MCB, and to ensure that no unexpected changes occurred during cell-line adaptation that impacted the B-domain-deleted recombinant FVIII genes or transcripts. The analysis included Southern blot and Northern blot analyses, as well as DNA sequencing. Figure 2 shows the results of the Southern blot analysis evaluating the DNA integration pattern for the ReFacto MCB and the Xyntha/ReFacto AF MCB, which show identical hybridization patterns (Data on File, Wyeth Pharmaceuticals, Collegeville, PA, USA). The consistency of patterns between the Xyntha/ReFacto AF WCB and end-of-production samples establishes the stability of the cell line during production. These analyses clearly established that the MCBs are genotypically indistinguishable with respect to the integrated and amplified recombinant FVIII genes and their expressed transcripts.

To maintain cell viability during the production phase, the Xyntha/ReFacto AF manufacturing process uses the same bioreactor scale and perfusion equipment as the original process. As with the licenced process, the production phase is defined by a temperature shift and a switch to production medium. Media formulation changes have been made to accommodate product synthesis in the absence of albumin through rebalancing key compo-

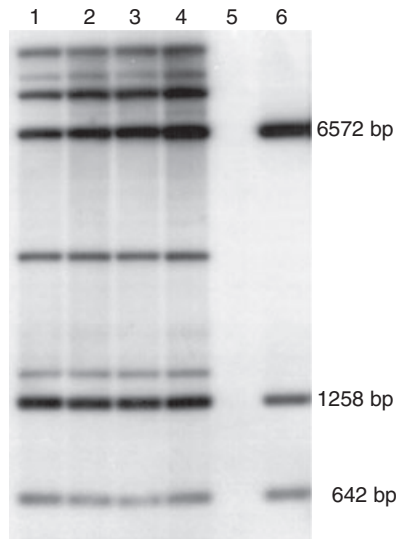


Fig. 2. Southern blot analysis of Xyntha/ReFacto AF cell banks. Two micrograms of genomic DNA isolated from ReFacto master cell bank (MCB) (lane 1), Xyntha/ReFacto AF MCB (lane 2) and working cell bank (WCB) (lane 3) cells were digested with Hind III restriction enzyme. Samples were size-fractionated by agarose gel electrophoresis, transferred to a membrane and hybridized to a ^{32}P -labelled B-domain deleted recombinant factor VIII (BDDrFVIII) probe. Lane 4 represents a Hind III digestion of genomic DNA isolated from cells obtained from the end of a Xyntha/ReFacto AF production campaign, lane 5 represents CHO genomic DNA control and lane 6 represents a control digest of the Xyntha/ReFacto AF expression vector.

nents and supplementing the media with additional nutrients, but similar bioreactor control strategies are used to maintain the cells in an optimal state for product synthesis.

The major purification process modifications are the replacement of the immunoaffinity chromatography step with an affinity step using a chemically synthesized polypeptide ligand and the introduction of a VRF step.

The immunoaffinity chromatography step used in the original ReFacto manufacturing process provides excellent removal of such process-related impurities as DNA and host cell proteins (HCPs) [2]. By replacing the mAb with a peptide ligand, higher column-loading capacities and improved resin cleaning afforded by a broader sanitization solution compatibility can be achieved [4]. Most notably, the peptide can be chemically synthesized, eliminating the requirement for a mAb derived from murine hybridoma culture and thereby removing the potential for introduction of an adventitious virus, such as an infectious retrovirus (known to be associated with hybridoma cultures) into the FVIII product stream [5–7].

Several peptides were identified by screening a bacteriophage display library expressing approximately 100 million unique peptides as amino-terminal fusions to the P3 coat protein. These peptides were designed to have five to seven residues between the cysteine residues, which oxidize to form a disulfide bond that results in a constrained ring. The peptide that was ultimately selected, designated TN8.2, was one of a family of related peptides derived from the library containing eight residues, including the cysteines, in the ring. The TN8.2 peptide contains 27 amino acids and includes a flexible linker to provide accessibility of the constrained ring for FVIII binding [4]. Figure 3 illustrates the selected residues of the ring and two flanking residues external to the cysteine bond, which were also variegated in the peptide library [4]. The peptide has an acetylated N-terminus and no primary amines, with the exception of a C-terminal lysine residue. This allows for efficient, site-directed immobilization of the peptide via the C-terminal lysine by the amine reactive N-Hydroxysuccinimide immobilization chemistry [4].

The peptide binds to the B-domain deleted recombinant FVIII (BDDrVIII) through the C2 domain of the 80-kD light chain portion of the BDDrVIII heterodimer. The interaction between BDDrVIII and the peptide is relatively weak, with a dissociation constant of $\sim 10^{-6}$ M, compared with the mAb that has a substantially lower kD of $\sim 10^{-10}$ M. This weak binding is overcome by immobilizing the peptide at approximately 125 times the molar concentration of the antibody, thus providing sufficient binding due to mass action. Figure 4 shows the binding isotherm for the immobilized peptide and BDDrVIII. The data show excellent fit to a Langmuir isotherm ($r^2 = 0.99$), indicating a single mode of interaction, without protein-protein interactions, and a dissociation constant of $0.92 \mu\text{M}$ [4].

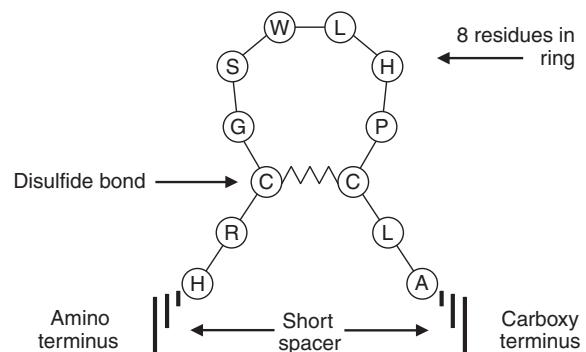


Fig. 3. TN8.2 ligand schematic. TN8.2 [4]. Sequence: Ac-AEGTGDHRCGSWLHPCLAEPEGGGSK-CO₂.

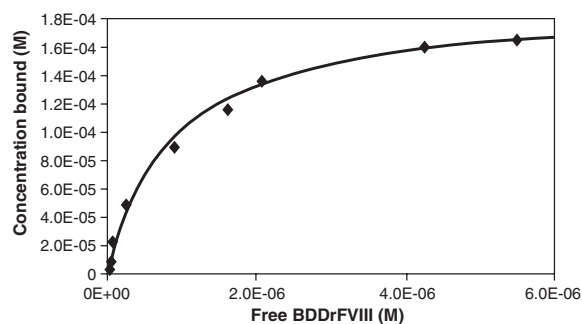


Fig. 4. Equilibrium binding measurement for the TN8.2 and B-domain deleted recombinant factor VIII (BDDrFVIII) interaction measured on TN8.2 Sepharose resin [4]. The equilibrium-binding isotherm was determined using repeated BDDrFVIII challenges to a resin sample; 50 μ L of a 50% slurry of resin was combined with 450 μ L of a BDDrFVIII solution and binding allowed to approach equilibrium (generally 30 min). The resin supernatant was then removed and replaced with another 450 μ L of BDDrFVIII solution. This process was repeated until the concentration of BDDrFVIII in the supernatant solution approached that of the challenge solution. Bound protein was determined from the difference between the units offered and the units remaining in the supernatant solution at equilibrium for each BDDrFVIII challenge using a chromogenic FVIII activity assay.

The screening conditions for peptide selection closely mimicked the operating conditions for the immunoaffinity chromatography step [8]. This made substitution of the immunoaffinity step with the TN8.2 chromatography resin relatively straightforward. The chromatographic characteristics of the immobilized peptide are very similar to the immunoaffinity resin. Table 1 compares the most relevant performance characteristics of both resins [8]. The resins have very nearly identical performance with respect to product quality attributes, i.e. product capture and impurity removal. The immobilized peptide performs better with respect to the more practical aspects of performance, i.e. recovery, capacity and cleaning conditions. The process pool derived from the TN8.2 Sepharose step is highly pure, based on sodium dodecyl sulphate–polyacryl-

amide gel electrophoresis (SDS–PAGE) analysis (see Fig. 5), with all of the protein impurities detected by SDS–PAGE in the load to this step removed during processing [4,8].

The goal of the new VRF step is elimination of noninfectious retroviral-like particles and potential adventitious viruses by means of the optimally sized 35-nm pore-size filter [9]. The single-use VRF device retains viral particles based on sieving properties, while allowing passage of the Xyntha/ReFacto AF protein. The virus filter was selected to provide robust clearance of such large viruses as retroviruses. The product passes freely through the membrane pores into the permeate, whereas viral particles, if present, are retained by the membrane. Filters with a smaller pore size, which have the capacity to retain parvoviruses, gave rise to variable product retention and subsequent yield losses (Data on File, Wyeth Pharmaceuticals). The VRF step was intentionally placed after the Q-Sepharose chromatography step because this process intermediate has no detergent present, which might complicate the operation of a filtration step, thereby enabling consistent performance of the VRF.

The battery of purity tests performed on the ReFacto MCB was designed in accordance with the guidelines provided in several regulatory documents [10–12]. Monitoring for adventitious viruses utilizes *in vitro* testing on indicator cell lines, which have been shown to be sensitive to a broad range of viruses, especially to those that are known to infect Chinese hamster ovary (CHO) cells. Lot-to-lot coverage for adventitious contamination during production is provided by testing unprocessed bulk (cells plus the conditioned medium) taken on the final harvest day of the manufacturing run. Additional coverage for minute virus of mice (MVM), a reported contaminant of some industrial CHO cell production cultures, is provided by using either an *in vitro* assay with an indicator cell line susceptible to MVM infection (324K or A9) or an MVM polymerase

Table 1. Comparison of TN8.2 and immunoaffinity purification step performance [8].

	Immunoaffinity	TN8.2
BDDrFVIII recovery (average of >10 cGMP runs)	63	85
CHO protein removal (\log_{10} reduction)	3.7	4.0
DNA removal (\log_{10} reduction)	4.1	4.1
BDDrFVIII informs captured	M_r 170 000 fusion protein + multiple heterodimer forms	M_r 170 000 fusion protein + multiple heterodimer forms
Elution peak volume (column volumes)	<1.0	<1.5
Dynamic capacity – (IU mL ⁻¹)	20 000 (estimate)	180 000
Process control loading limit (IU mL ⁻¹)	5000	25 000
Sanitization solution	0.1 M acetic acid, 20% ethanol, pH 4.0	6 M GuHCL 50 mM acetic acid, pH 3.0

chain reaction analysis [13]. No adventitious viruses were detected when the MCB samples were tested using any of the *in vitro* or *in vivo* methods. Furthermore, no infectious retrovirus activity was detected in the cocultivation assay. Transmission electron microscopy showed the cells to be free of all virus-like particles other than the type A and C particles previously reported to be present at low levels in CHO cells [14–16]. On the basis of these results, it was concluded that no detectable adventitious microbial or viral agents had been introduced into the Xyntha/ReFacto AF MCB and that no infectious retroviruses were present.

The purification steps of the Xyntha/ReFacto AF process were also evaluated for their ability to remove or inactivate model viruses. The Xyntha/ReFacto AF viral clearance and inactivation studies were designed and executed in accordance with regulatory guidelines [12]. At least two orthogonal modes of clearance were identified for each virus evaluated in this study. This study used a panel of model viruses with an emphasis on viruses known to infect CHO cells (see Table 2). These viruses include three enveloped viruses [parainfluenza virus (PI-3), pseudorabies virus (PRV), and xenotropic murine leukaemia virus (X-MuLV)] and two nonenveloped viruses [MVM and Reovirus-3 (Reo-3)] (Data on File, Wyeth Pharmaceuticals). The model viruses used in this evaluation were selected to cover a wide variety of virus families that differ by size, genome type, envelope and resistance to physicochemical inactivation. The panel of viruses used in this assessment differs from those used in the assessment of the original process [3,4], reflecting a shift in focus from viruses representing adventitious agents that could potentially be present in the HSA used in the original cell culture medium, to a panel that is typically used to evaluate recombinant protein production via a process devoid of animal- or human-derived raw materials [17,18].

As a result of the importance of the TN8.2 Sepharose and Planova 35N VRF steps in ensuring the viral safety of the product, viral clearance studies were performed for these steps for all five viruses in the panel. For the S/D virus inactivation step, runs were conducted for each of the three enveloped viruses. The demonstration of comparable performance of the laboratory scale to the manufacturing scale for each step establishes the laboratory-scale systems as valid models of the manufacturing steps for use in virus validation studies. For the TN8.2 Sepharose step, both unused and used resins were tested because of the importance of the affinity chromatography step in the viral safety package. Each chromatography eluate included the virus present in the prepeak, peak and postpeak fraction, as a worst-case estimate. The ratio and temperature of the S/D chemicals were at the lowest acceptable levels, and the VRF permeate included the virus present in the maximum filter flush volume, representing the worst-case conditions for the relevant step.

Table 2 illustrates the results of the virus validation studies. A significant reduction in the virus titre was observed for all TN8.2 Sepharose runs, with the majority of virus particles removed in the load eluate and washes. These results demonstrate that the mechanism of removal was consistent with affinity chromatography, where, due to the specificity of binding between the ligand (TN8.2) and the desired product (Xyntha/ReFacto AF), impurities do not bind to the column or are weakly retained and removed prior to product elution. The performance of unused and used TN8.2 Sepharose resins was also consistent. The S/D step provided instantaneous and complete inactivation of the three enveloped viruses tested. The VRF step provided significant removal of all viruses tested with the exception of MVM, which was the smallest virus tested and would be expected to pass through the 35-nm pore of this filter. The

Table 2. Results of virus clearance studies (Data on File, Wyeth Pharmaceuticals, Collegeville, PA, USA).

Virus	SP Sepharose	S/D Inactivation	TN8.2 Sepharose	Q Sepharose	Planova 35N Nanofiltration	Butyl Sepharose	Total LRV*
MuLV	ND	>3.24	>2.99	ND	>5.18	ND	>11.4
MMV	1.46	ND	2.52	0.52*	0.63*	1.23	5.2
PI-3	ND	>4.93	1.51	ND	>4.95	ND	>11.4
Reo-3	ND	ND	4.40	ND	>5.93	ND	>10.3
PRV	ND	>4.90	3.13	ND	>6.00	ND	>14.0

*Log reduction values (LRV) <1.0 are not included in the calculation of total LRV.

ND, not done; Butyl, Butyl-Sepharose; env, enveloped; LRV, log removal value; MVM, minute virus of mice; nonenv, nonenveloped; PI-3, parainfluenza virus; PRV, pseudorabies virus; Reo-3, Reovirus-3; S/D, solvent/detergent; SP, SP-Sepharose; VRF, virus removal filtration; X-MuLV, xenotropic murine leukaemia virus.

total reduction across all the tested steps was between 5.2 and >10.3 log for the nonenveloped viruses, and between >11.4 and >14.0 log for the enveloped viruses. The total log removal values (LRVs) for all the tested viruses are quite high, with consistency between duplicates for all steps, which demonstrates that the purification process provides excellent assurance of removal and inactivation of model viruses. The overall inactivation and removal package compares favourably with the package for the original process; the Xyntha/ReFacto AF process has higher total LRV for MuLV, higher LRVs for nonenveloped virus (i.e. Reo-3) and incorporates the addition of a third robust step for virus clearance (i.e. Planova 35N VRF) (Data on File, Wyeth Pharmaceuticals).

Process validation

The Xyntha/ReFacto AF manufacturing process was validated to ensure effective and consistent performance within the established limits of the operating parameters. Although the albumin-free cell culture (AFCC) manufacturing process is quite similar to the original ReFacto process, a significant duplication of the process validation package was undertaken to provide a clear comparison of performance and consistency between the two processes.

Compared with those of the original ReFacto process, the cell culture growth and production phases of the Xyntha/ReFacto AF manufacturing process demonstrate consistent and adequate rates and densities of cell growth, cell removal and harvest operations. Cell culture robustness has been established using laboratory studies that test critical control parameter limits and show acceptable performance and product quality.

In-process, cell culture limits are unchanged relative to the original ReFacto manufacturing process for all critical parameters, except for minor adjustments in the temperature of the seed bioreactor, the dissolved oxygen of the production bioreactor, the inoculum densities of the seed bioreactor and production bioreactors and the cumulative cell age during production. Cell culture robustness studies were conducted in either small shake flasks or 2-L laboratory bioreactors, which have both been qualified as appropriate scale-down models of the full-scale bioreactor.

Stability studies were performed to ensure that the cell culture medium could be stored for a sufficient period to allow routine manufacturing prior to use. To assess the stability of an extended lineage of Xyntha/ReFacto AF WCB cells at the end of their

validated cell age, the WCB cells at this age limit were used to inoculate a production bioreactor for the synthesis of the clinical drug substance. All in-process control parameters were achieved during the course of this cell-culture production run. Characterization of the drug-substance batches manufactured from this run showed that the drug substance that was produced met all release specifications. Together with additional cell-line characterization data from Southern and Northern blot hybridizations and DNA sequencing analyses, these studies support the *in vitro* age limit of the Xyntha/ReFacto AF WCB cells.

The purification process has been validated for removal of host cell-derived, media-derived and purification process-derived impurities [2] (Data on File, Wyeth Pharmaceuticals). The pattern of CHO protein removal by the Xyntha/ReFacto AF purification process is very similar to that of the original process. The most efficient step for removing host cell-derived impurities is the affinity chromatography step (AFCC uses the TN8.2 Sepharose resin) [2]. During the AFCC process, 3.4-log removal of CHO protein was consistently demonstrated. The subsequent Q-Sepharose step provides an additional 1.2-log removal, and the remaining Butyl-Sepharose and Superdex 200 steps contribute a combined reduction of 0.8 log (see Table 3). The pattern of DNA removal by the Xyntha/ReFacto AF purification process is also very similar to that of the original manufacturing process. A 3.9-log removal of DNA has been consistently demonstrated for the TN8.2 Sepharose step (Data on File, Wyeth Pharmaceuticals). The Q-Sepharose step provides an additional >1.9 log removal. The removal across the Butyl-Sepharose and Superdex 200-pg chromatography steps could not be shown to contribute to the reduction, as the

Table 3. HCP Removal (Data on File, Wyeth Pharmaceuticals, Collegeville, PA, USA).

Batch	TN8.2 eluate (LRV)	Q eluate (LRV)	HIC eluate (LRV)	GF eluate (LRV)	Total (LRV)
1	3.3	1.1	0.4	0.5	5.4
2	3.3	1.2	0.5	0.4	5.5
3	3.5	1.4	0.6	0.3	5.8
4	3.6	1.2	0.6	0.3	5.7
5	3.3	1.1	0.3	0.4	5.1
6	3.3	1.3	0.4	0.3	5.2
7	3.5	1.1	0.4	0.3	5.3
8	3.3	1.0	0.4	0.3	5.0
Mean	3.4	1.2	0.4	0.4	5.4

GF, gel filtration; HCP, host cell protein; HIC, hydrophobic interaction chromatography; LRV, log removal value; Q, Q-Sepharose.

DNA levels at this stage are below the limit of detection of the assay [2] (Data on File, Wyeth Pharmaceuticals). Overall, the purification process removes DNA to levels below the limit of $<14 \text{ pg } 1000 \text{ IU}^{-1}$ of drug substance (Data on File, Wyeth Pharmaceuticals). This level is significantly lower than current World Health Organization recommended levels of $<100 \text{ pg}$ per dose of cellular DNA [10].

Process-derived impurities are introduced into the product stream by purification process buffers and resins. The removal of a representative set of these components was validated, including ethylenediaminetetraacetic acid (EDTA), tri-n-butyl-phosphate (TNBP), Octoxynol 9, TN8.2 ligand, ethylene glycol and ammonium acetate (Data on File, Wyeth Pharmaceuticals). The safety of the Xyntha/ReFacto AF drug substance with respect to the TN8.2 ligand residuals has been established by a combination of

acute toxicology studies performed on the TN8.2 ligand, along with a comprehensive validation package addressing the consistency of TN8.2 ligand leaching and removal. The validation package combines concurrent removal studies for cGMP batches and small-scale spike and removal studies. The small-scale spike/removal studies demonstrated a minimum of a 2.0-log reduction for the Q-Sepharose step and a 0.8-log reduction for the Butyl-Sepharose step [4]. All batches of the drug substance had no detectable TN8.2 (calculated to be $<5.7 \text{ ng mL}^{-1}$) (Data on File, Wyeth Pharmaceuticals). To put this level into perspective, in an acute toxicology study conducted in Sprague-Dawley rats and used to support both the IND and the licensure application, the levels of TN8.2 peptide tested were 300 million-fold higher than the maximum TN8.2 residual level that could be contained in a 2000-IU dose (corresponding to a ≥ 8.3 -log safety margin). Even at the level tested in the rats, there were no effects observed in the toxicity study [4].

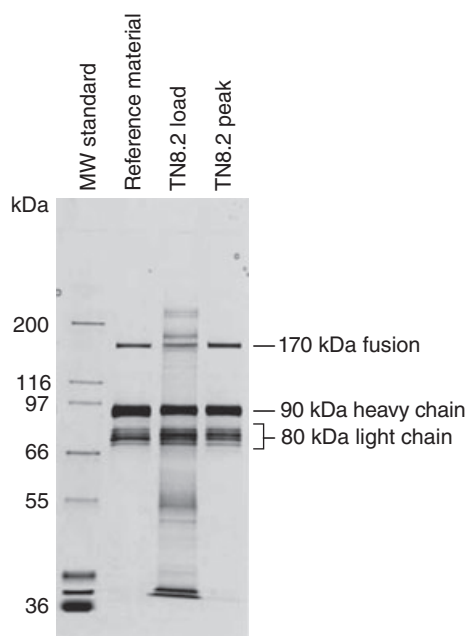


Fig. 5. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of TN8.2 Sepharose load and purified Xyntha/ReFacto AF [8]. Silver stained reducing SDS-PAGE of the TN8.2 Sepharose load and peak fraction compared with purified Xyntha/ReFacto AF reference material. The TN8.2 Sepharose load represents clarified conditioned media containing Xyntha/ReFacto AF that has been processed over a SP-Sepharose column followed by treatment with a solvent-detergent mixture. The TN8.2 peak represents the elution of TN8.2 column using an ethylene glycol solution. The major Xyntha/ReFacto AF isoforms are represented by the 170 kDa product of the translational fusion expression vector and the 90 kDa heavy chain and the 80 kDa light chain of the fully processed protein.

Stability, comparability overview and clinical evaluation of Xyntha/ReFacto AF

The formulations for both the drug substance and the drug product were not changed for the Xyntha/ReFacto AF process. This minimizes the likelihood of any changes in the drug substance or product stability profiles, as the improved manufacturing process provides material that is comparable in purity and quality to that of the original process. To confirm these expectations, stability studies were conducted on three batches of commercial final drug product and three batches of intermediate drug substance. The commercial material was monitored through 36 months, which is the current shelf-life for Xyntha/ReFacto AF (Data on File, Wyeth Pharmaceuticals). Accelerated studies at higher temperatures were also performed for both the final drug product and the intermediate drug substance and were monitored through 6 months. Several parameters were assessed in both the long- and short-term studies, including identity, potency, purity and quality. The assays and specifications used in the stability programme for the Xyntha/ReFacto AF drug substance are a subset of the analytic procedures performed at release because they are indicative of stability. Results of the assays used to monitor the stability of final drug product and intermediate drug substance during storage for all validation batches demonstrate no significant changes in terms of potency, quality or purity for Xyntha/ReFacto AF (Data on File, Wyeth Pharmaceuticals).

A complete and comprehensive programme was designed to compare ReFacto and Xyntha/ReFacto AF on both structural and functional bases. Comparisons of the various sources of Xyntha/ReFacto AF were also conducted: nonclinical, clinical and commercial materials (Data on File, Wyeth Pharmaceuticals; Personal communication, M. Jankowski). The overall assessment evaluated the following complementary elements: process comparability (cell culture and purification), drug-substance release testing data, detailed structural characterization and analysis, *in vitro* functional analysis and forced decomposition analysis. Shown in Fig. 6 is a comparative analysis using SDS-PAGE of representative ReFacto and Xyntha/ReFacto AF, demonstrating the high degree of similarity between the two materials (Data on File, Wyeth BioPharma).

Pivotal clinical studies were initiated to meet the requirements for the approval of a new FVIII product. These clinical studies were designed to meet

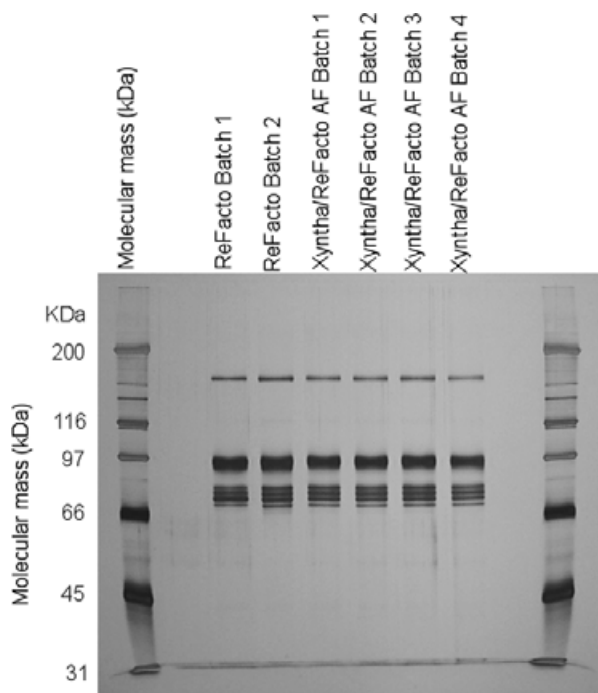


Fig. 6. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of purified ReFacto and Xyntha/ReFacto AF. Silver stained reducing SDS-PAGE of representative ReFacto and Xyntha/ReFacto AF drug substance batches. Approximately 1 µg of each sample was reduced with dithiothreitol (DTT) prior to analysis. The 6.5% SDS-PAGE was performed using standard Laemmli conditions. The major ReFacto and Xyntha/ReFacto AF isoforms are represented by the 170 kDa product of the translational fusion expression vector and the 90 kDa heavy chain and the 80 kDa light chain of the fully processed protein.

FDA requirements for FVIII product, which include (i) a comparative pharmacokinetics (PK) study and (ii) an efficacy/safety study in previously treated patients (PTPs). The PK profile of Xyntha/ReFacto AF vs. FLrFVIII was assessed in a randomized, double-blind, crossover study of 30 PTPs using the one-stage clotting assay. In addition, the safety and efficacy of Xyntha/ReFacto AF were assessed in a total of 94 PTPs during 6 months of prophylaxis supplemented with on-demand treatment. A follow-up PK study was conducted after 6 months [18,19].

Ninety percent (90%) confidence intervals about the ratios of the geometric least square mean values of key PK parameters (AUC_{∞} , AUC_t and K value) were within the bioequivalence window of 80–125%, demonstrating the PK equivalence of Xyntha/ReFacto AF and Advate. Of the 94 patients, two had transient, low-titer, *de novo*, clinically silent inhibitors, both of which were negative on follow-up testing. This study also demonstrated that the Xyntha/ReFacto AF manufacturing process did not affect PK, safety or efficacy outcomes in a clinical setting [19].

Discussion

The Xyntha/ReFacto AF manufacturing process was designed to maximize the viral safety profile of the product and minimize the probability of any observable changes relative to the product derived from the original process. The key changes to the cell culture steps of the manufacturing process were focused on removing animal- and human-derived raw materials in the MCB and the cell culture medium. The purification process eliminated the use of a hybridoma-derived murine mAb and introduced a VRF step. The Xyntha/ReFacto AF purification process is the first to use a chemically synthesized polypeptide for purification of FVIII. The product formulation was unchanged to ensure that the stability profile of the various dosages would remain at the limits established with the original licenced process.

This conservative set of changes was limited in scope to avoid any unintentional impact on product characteristics that could influence the PK profile, clinical efficacy and/or safety. A strong biochemical and biophysical comparability package supports the unchanged nature of the ReFacto product, despite these process improvements. Multiple clinical trials conducted with ReFacto produced by the AFCC process proved that ReFacto manufactured via this third-generation technique was safe and efficacious. A double-blind, randomized PK crossover study

demonstrated that Xyntha/ReFacto AF was PK-equivalent to a full-length rFVIII, and routine prophylaxis with Xyntha/ReFacto AF was found to be effective in preventing haemorrhages in patients with pre-existing target joint(s) [20].

A comprehensive and complete process validation programme was conducted to ensure product safety and process consistency. Following international guidelines for recombinant protein production, all steps in the cell culture and purification processes were evaluated and appropriate process control ranges were established. The clinical programme used several lots of drug substance and drug product produced at full scale in the commercial manufacturing plant, confirming the consistency of the Xyntha/ReFacto AF process.

The combination of these process design elements, comparability assessments, clinical studies and process validation studies provides assurance of the safety and process consistency of the Xyntha/ReFacto AF process.

Acknowledgements

The authors would like to thank the following past and present Wyeth BioPharma staff members: Denis Drapeau, Gene Lee, Martin Sinacore, Molly Tannatt, Ed Fritsch, Jeff Deetz, Priscilla Jennings, Dick Wright, Suresh Vunnum, Jeffrey Robinson and Denise O'Hara. Additional thanks to our colleagues at Biovitrum, including Ake Ljungvist, Lotta Ljungqvist, Anna Messing-Eriksson, Christine Wesström, Bertil Eriksson and Mats Jernberg. Collaborators at Dyax Corporation included Thomas Ransohoff, Daniel Potter, Art Ley and Bruce Dawson. This work is dedicated to the memories of Sigrid and Daniel, who are both greatly missed by all of their collaborators and friends.

Disclosures

M. Jankowski and J. Booth are employees of Wyeth.

References

- 1 Meeks SL, Josephson CD. Should hemophilia treaters switch to albumin-free recombinant factor VIII concentrates. *Curr Opin Hematol* 2006; 13: 457–61.
- 2 Eriksson RK, Fenge C, Lindner-Olsson E *et al.* The manufacturing process for B-domain deleted recombinant factor VIII. *Semin Hematol* 2001; 38(2 Suppl. 4): 24–31.
- 3 Charlebois TS, O'Connell BD, Adamson SR *et al.* Viral safety of B-domain deleted recombinant factor VIII. *Semin Hematol* 2001; 38(2 Suppl. 4): 32–9.
- 4 Kelley BD, Tannatt M, Magnusson R, Hagelberg S, Booth J. Development and validation of an affinity chromatography step using a peptide ligand for cGMP production of factor VIII. *Biotechnol Bioeng* 2004; 87: 400–12.
- 5 Adamson SR. Experiences of virus, retrovirus and retrovirus-like particles in Chinese hamster ovary (CHO) and hybridoma cells used for production of protein therapeutics. *Dev Biol Stand* 1998; 93: 89–96.
- 6 Bartal AH, Feit C, Erlandson RA, Hirshaut Y. Detection of retroviral particles in hybridomas secreting monoclonal antibodies. *Med Microbiol Immunol* 1986; 174: 325–32.
- 7 Machala O, Mach O, Bubenik J, Hasek M. The presence of retroviral particles in hybridoma cell lines. *Folia Biol (Praba)* 1986; 32: 178–82.
- 8 Kelley BD, Booth J, Tannatt M *et al.* Isolation of a peptide ligand for affinity purification of factor VIII using phage display. *J Chromatogr A* 2004; 1038: 121–30.
- 9 Jakubik JJ, Vicik SM, Tannatt MM, Kelley BD. West Nile Virus inactivation by the solvent/detergent steps of the second and third generation manufacturing processes for B-domain deleted recombinant factor VIII. *Haemophilia* 2004; 10: 69–74.
- 10 Department of Health and Human Services, Public Health Services, Center for Biologics Evaluation and Research. *Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals* 1993. Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM062745.pdf> (accessed 8 December 2009).
- 11 European Medicines Agency. ICH Topic Q 5 D quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products. London: EMEA, 1998:1–13.
- 12 European Medicines Agency. ICH Topic Q 5 A (R1) quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin. London: EMEA, 1997: 1–29.
- 13 Chang A, Havas S, Borellini F, Ostrove JM, Bird RE. A rapid and simple procedure to detect the presence of MVM in conditioned cell fluids or culture media. *Biologicals* 1997; 25: 415–9.
- 14 Lieber MM, Benveniste RE, Livingston DM, Todaro GJ. Mammalian cells in culture frequently release type C viruses. *Science* 1973; 182: 56–9.
- 15 Thion C, Green M. Cyclic AMP-amplified replication of RNA tumour virus-like particles in Chinese hamster ovary cells. *Nat New Biol* 1973; 244: 227–31.
- 16 Lubiniecki AS, May LH. Cell bank characterization for recombinant DNA mammalian cell lines. *Dev Biol Stand* 1985; 60: 141–6.
- 17 Adamson S, Charlebois T, O'Connell B, Foster W. Viral safety of recombinant factor IX. *Semin Hematol* 1998; 35(2 Suppl. 2): 22–7.
- 18 Wyeth Pharmaceuticals Inc. XYNTHA™ [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free] For Intravenous Use, Freeze-Dried Powder Full *Prescribing Information*. Philadelphia, PA, 2008.
- 19 Recht M, Nemes L, O'Brien AC, Udata C, Roth D, Arkin S. ReFacto AF Is effective and safe in previously treated patients with severe hemophilia A: final results of a pivotal phase III study. *Blood* 2007; 110: 349a.
- 20 Recht M, Nemes L, Matysiak M *et al.* Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of hemophilia A: demonstration of safety, efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII. *Haemophilia* 2009; 15: 869–80.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XYNTHA® (antihemophilic factor [recombinant]) lyophilized powder for solution, for intravenous injection

Initial U.S. Approval: 2008

INDICATIONS AND USAGE

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

DOSAGE 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. (2.1)
- Frequency of XYNTHA administration is determined by the type of bleeding episode and the recommendation of the treating physician. (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Do not use in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster proteins. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

- The most common adverse reactions (≥10%) with XYNTHA in adult and pediatric previously treated patients (PTPs) were headache, arthralgia, pyrexia, and cough. (6)
- Across all studies, 4 subjects developed factor VIII inhibitors (2.4%). (6.2)

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

USE IN SPECIFIC POPULATIONS

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. (8.4)

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

Revised: 8/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dose
 - 2.2 Preparation and Reconstitution
 - 2.3 Administration
 - 2.4 Use of a XYNTHA Vial Kit and a XYNTHA SOLOFUSE Kit
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Hypersensitivity Reactions
 - 5.2 Neutralizing Antibodies
 - 5.3 Monitoring Laboratory Tests
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
 - 6.2 Immunogenicity
 - 6.3 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

- On-demand treatment and control of bleeding episodes
- Perioperative management

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

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Titrate the administered doses to the patient's clinical response.
- One International Unit (IU) of factor VIII activity corresponds approximately to the quantity of factor VIII in one milliliter of normal human plasma. The calculation of the required dosage of factor VIII is based upon the empirical finding that, on average, 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by approximately 2 IU/dL.²

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

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

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

On-demand treatment and Control of Bleeding Episodes

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

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

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy
Minor Early hemarthrosis, minor muscle or oral bleeds.	20-40	12-24	At least 1 day, depending upon the severity of the bleeding episode.
Moderate Bleeding into muscles. Mild head trauma. Bleeding into the oral cavity.	30-60	12-24	3-4 days or until adequate local hemostasis is achieved.
Major Gastrointestinal bleeding, Intracranial, intra-abdominal, or intrathoracic bleeding. Fractures.	60-100	8-24	Until bleeding is resolved.

Perioperative Management

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

Table 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor Minor operations, including tooth extraction.	30-60	12-24	3-4 days or until adequate local hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major Major operations.	60-100	8-24	Until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved.

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:

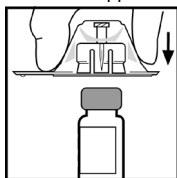
- If the patient uses more than one vial of XYNTHA per infusion, reconstitute each vial according to the following instructions. Remove the diluent syringe, leaving the vial adapter in place. Use a separate 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted 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

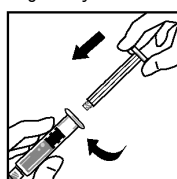
1. Allow the XYNTHA vial and the prefilled diluent syringe to reach room temperature.
2. Remove the plastic flip-top cap from the XYNTHA vial to expose the central portions of the rubber stopper.



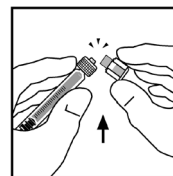
3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any surface.
4. Peel back the cover from the clear plastic vial adapter package. **Do not remove the adapter from the 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.



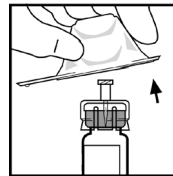
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.



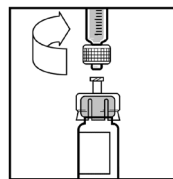
7. Break off the tamper-resistant plastic tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted XYNTHA immediately), so place the cap on its top on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



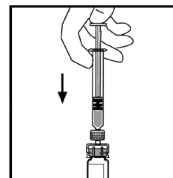
8. Lift the package away from the adapter and discard the package.



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.



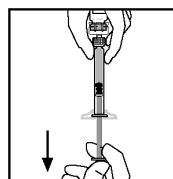
10. Slowly depress the plunger rod to inject all the diluent into the XYNTHA vial.



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.**

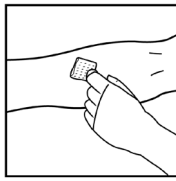
2.3 Administration

For intravenous infusion after reconstitution only.

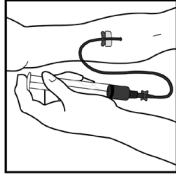
Inspect the final XYNTHA solution visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear to slightly opalescent and colorless. If it is not, discard the solution and use a new kit.

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.



- 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.
- Inject the reconstituted XYNTHA product intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.



- 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.

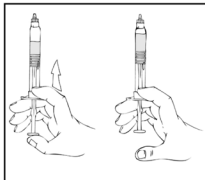
2.4 Use of a XYNTHA Vial Kit with a XYNTHA SOLOFUSE Kit

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.

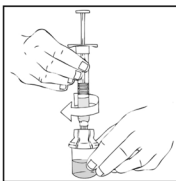
- Reconstitute the XYNTHA vial using the instructions described in Preparation and Reconstitution [see *Dosage and Administration (2.2)*].
- Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the XYNTHA vial with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



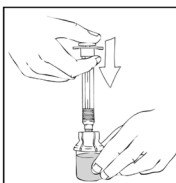
- Reconstitute the XYNTHA SOLOFUSE using the instructions included with the product kit, remembering to remove most, but not all, of the air from the drug product chamber.



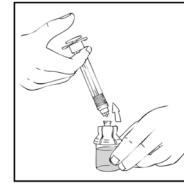
- After removing the protective blue vented cap, connect the XYNTHA SOLOFUSE to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.



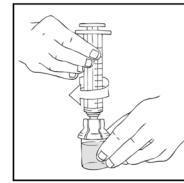
- Slowly depress the plunger rod of the XYNTHA SOLOFUSE until the contents empty into the XYNTHA vial. The plunger rod may move back slightly after release.



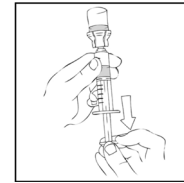
- Detach and discard the empty XYNTHA SOLOFUSE from the vial adapter.
Note: If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.



- 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.



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



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

Each XYNTHA vial 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)*].^{4,5,6,7,8,9,10,11,12}

5.3 Monitoring Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

XYNTHA was evaluated in five completed clinical studies (N=178), comprising four studies with adult and pediatric PTPs.

The safety and efficacy of XYNTHA was evaluated in two completed pivotal studies. In the first study (n=94), safety and efficacy were examined in PTPs with severe to moderately severe hemophilia A (factor VIII activity in plasma [FVIII:C] $\leq 2\%$) who received XYNTHA for routine prophylaxis and on-demand treatment. Ninety-four subjects received at least one dose of XYNTHA, resulting in a total of 6,775 infusions [see *Clinical Studies (14)*]. The second study (n=30) examined the use of XYNTHA for surgical prophylaxis in PTPs with severe to moderately severe hemophilia A (FVIII:C $\leq 2\%$) who required elective major surgery and were expected to receive XYNTHA replacement therapy for at least 6 days post-surgery. All subjects received at least one dose of XYNTHA, resulting in 1,161 infusions. One subject received XYNTHA for a pre-surgery pharmacokinetic assessment only and did not undergo surgery [see *Clinical Studies (14)*].

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

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

6.2 Immunogenicity

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

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

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

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

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

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

6.3 Postmarketing Experience

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

The following postmarketing adverse reaction has been reported for XYNTHA:

Inadequate therapeutic response

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

In the first completed open-label safety and efficacy study of XYNTHA (n=94), of the 18 adolescent subjects 12 to <17 years of age with severe to moderately severe hemophilia A (FVIII:C $\leq 2\%$), who were previously treated with at least 150 EDs to FVIII products, 10 subjects received XYNTHA for on-demand and follow-up treatment. The median dose per on-demand infusion was 47 IU/kg (min-max: 24-74) and the median exposure per subject was 6 days (min-max: 1-26).

Of the 18 subjects <17 years of age who received at least 1 dose of XYNTHA, 10 subjects had bleeding episodes during the study. A total of 66 bleeding episodes were treated with on-demand infusions of XYNTHA. The majority of the bleeding episodes (63/66 or 95%) resolved with 1 or 2 infusions. The response to infusion was rated on a pre-specified 4 point hemostatic efficacy scale. Thirty-eight (38) of 66 bleeding episodes (58%) were rated excellent or good in their response to initial treatment, 24 (36%) were rated as moderate, and 4 (6%) were not rated.

Additional data for 50 subjects are available from a second safety and efficacy study of XYNTHA in children <16 years of age with severe to moderately severe hemophilia A (FVIII:C $\leq 2\%$) and with at least 20 prior EDs to FVIII products. Of the 50 subjects, 38 subjects received XYNTHA for on-demand and follow-up treatment of bleeding episodes. The median dose per on-demand infusion was 28 IU/kg (min-max: 10-92) and the median exposure per subject was 9 days (min-max: 1-95).

Of the 50 subjects <16 years of age who received at least 1 dose of XYNTHA, 38 had 562 bleeding episodes during the study. The majority of the bleeding episodes (518/562 or 92%) resolved with 1 or 2 infusions. Of 559 bleeding episodes treated with XYNTHA with response assessments to the first infusion, 526 (94%) were rated excellent or good in their response to initial treatment and 27 (5%) were rated as moderate.

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

11 DESCRIPTION

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

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

Parameter	Initial Visit (n = 30)	Month 6 (n = 25)	Pre-surgery (n=8)
C _{max} (IU/mL)	1.08 ± 0.22	1.24 ± 0.42	1.08 ± 0.24
AUC _∞ (IU·hr/mL)	13.5 ± 5.6	15.0 ± 7.5	16.0 ± 5.2
t _{1/2} (hr)	11.2 ± 5.0	11.8 ± 6.2*	16.7 ± 5.4
CL (mL/hr/kg)	4.51 ± 2.23	4.04 ± 1.87	3.48 ± 1.25
V _{ss} (mL/kg)	66.1 ± 33.0	67.4 ± 32.6	69.0 ± 20.1
Recovery (IU/dL per IU/kg)	2.15 ± 0.44	2.47 ± 0.84	2.17 ± 0.47

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

Table 4 shows the pharmacokinetic parameters of nine children; four aged 14 or 15 years of age, who are also included in the summary for the adults above, along with five children aged 3.7-5.8 years after single 50 IU/kg doses of XYNTHA. Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximately 40% higher in children.

Parameter	Young Children (n=5)	Adolescents (n=4)
Age (min - max, yr)	3.7 - 5.8	14 - 15
C _{max} (IU/mL)	0.78 ± 0.34	0.97 ± 0.21
AUC _∞ (IU·hr/mL)	12.2 ± 6.50	8.5 ± 4.0
t _{1/2} (hr)	8.3 ± 2.7	6.9 ± 2.4
CL (mL/hr/kg)	6.29 ± 4.87	6.62 ± 2.16
V _{ss} (mL/kg)	66.9 ± 55.6	67.1 ± 13.6
Recovery (IU/dL per IU/kg)	1.52 ± 0.69	1.95 ± 0.41

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

Two completed multicenter, open-label studies support the analysis of safety and efficacy of XYNTHA in on-demand treatment and control of bleeding episodes and perioperative management. These completed clinical studies for XYNTHA examined 124 PTP subjects, 94 for on-demand treatment and routine prophylaxis and 30 for surgical prophylaxis. Subjects with severe to moderately severe hemophilia A (FVIII:C ≤2%) and no history of FVIII inhibitors were eligible for the trials.

On-demand treatment and Control of Bleeding Episodes

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

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

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, min-max: 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%) occurred ≤48 hours after the last dose and 39% (70/180 bleeds) occurred >48 hours after the last dose. The majority of bleeds reported to occur ≤48 hours after the last prophylaxis dose were traumatic (64/110 bleeds or 58%). Forty-two bleeds (42/70 or 60%) reported to occur >48 hours after the last prophylaxis dose were spontaneous. The on-demand treatment dosing regimen was determined by the investigator. The median dose for on-demand treatment was 31 IU/kg (min-max: 6-74 IU/kg) and the median exposure per subject was 3 days (min-max: 1-26).

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

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

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

Perioperative Management

In a study (n=30) for surgical prophylaxis in subjects with hemophilia A, XYNTHA was administered to 25 efficacy-evaluable PTPs undergoing major surgical procedures (11 total knee replacements, 1 hip replacement, 5 synovectomies, 1 left ulnar nerve transposition release, 1 ventral hernia repair/scar revision, 1 knee arthroscopy, 1 revision and debridement of the knee after a total knee replacement, 1 hip arthroplasty revision, 1 stapes replacement, 1 ankle arthrodesis, and 1 pseudotumor excision).¹⁷

The results of the hemostatic efficacy ratings for these subjects are presented in Table 6. Investigator's ratings of efficacy at the end of surgery and at the end of the initial postoperative period were excellent or good for all assessments. Intraoperative blood loss was reported as "normal" or "absent" for all subjects. Thirteen of the subjects (13/25 or 52%) had blood loss in the postoperative period. The postoperative blood loss was rated as "normal" for ten of these cases while three cases were rated "abnormal" (1 due to hemorrhage following surgical trauma to the epigastric artery, 1 due to an 800 mL blood loss after hip replacement surgery, and 1 after an elbow synovectomy where the blood loss could not be measured by the investigator).

Table 6: Summary of Hemostatic Efficacy

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

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

15 REFERENCES

- Nilsson IM, Berntorp EE and Freiburghaus C. Treatment of patients with factor VIII and IX inhibitors. *Thromb Haemost.* 1993;70(1):56-59.
- Hoyer LW. Hemophilia A. *N Engl J Med.* 1994;330:38-47.
- Juhlin F. Stability and Compatibility of Reconstituted Recombinant Factor VIII SQ, 250 IU/ml, in a System for Continuous Infusion. Pharmacia Document 9610224, 1996.
- Ehrenforth S, Kreuz W, Scharrer I, et al. Incidence of development of factor VIII and factor IX inhibitors in hemophiliacs. *Lancet.* 1992;339:594-598.
- Lusher J, Arkin S, Abildgaard CF, Schwartz RS, the Kogenate PUP Study Group. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. *N Engl J Med.* 1993;328:453-459.
- Bray GL, Gomperts ED, Courter S, et al. A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. *Blood.* 1994;83(9):2428-2435.
- Kessler C, Sachse K. Factor VIII:C inhibitor associated with monoclonal-antibody purified FVIII concentrate. *Lancet.* 1990;335:1403.
- Schwartz RS, Abildgaard CF, Aledort LM, et al. Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. *N Engl J Med.* 1990;323:1800-1805.
- White GC II, Courter S, Bray GL, et al. A multicenter study of recombinant factor VIII (Recombinate™) in previously treated patients with hemophilia A. *Thromb Haemost.* 1997;77(4):660-667.
- Gruppo R, Chen H, Schroth P, et al. Safety and immunogenicity of recombinant factor VIII (Recombinate™) in previously untreated patients: A 7.3 year update. *Haemophilia.* 1998;4:228 (Abstract No. 291, XXIII Congress of the WFH, The Hague).
- Scharrer I, Bray GL, Neutzling O. Incidence of inhibitors in haemophilia A patients - a review of recent studies of recombinant and plasma-derived factor VIII concentrates. *Haemophilia.* 1999;5:145-154.
- Abshire TC, Brackmann HH, Scharrer I, et al. Sucrose formulated recombinant human antihemophilic Factor VIII is safe and efficacious for treatment of hemophilia A in home therapy: Results of a multicenter, international, clinical investigation. *Thromb Haemost.* 2000;83(6):811-816.
- Sandberg H, Almstedt A, Brandt J, Castro VM, Gray E, Holmquist L, et al. Structural and Functional Characterization of B-Domain Deleted Recombinant Factor VIII. *Sem Hematol.* 2001;38 (Suppl. 4):4-12.
- Kelley BD, Tannatt M, Magnusson R, Hagelberg S. Development and Validation of an Affinity Chromatography Step Using a Peptide Ligand for cGMP Production of Factor VIII. *Biotechnol Bioeng.* 2004;87(3):400-412.
- Mann KG and Ziedens KB. Overview of Hemostasis. In: Lee CA, Berntorp EE and Hoots WK, eds. *Textbook of Hemophilia.* USA, Blackwell Publishing; 2005:1-4.
- Recht M, Nemes L, Matysiak M et al. Clinical Evaluation of Moroctocog Alfa (AF-CC), a New Generation of B-Domain Deleted Recombinant Factor VIII (BDDrFVIII) for Treatment of Haemophilia A: Demonstration of Safety, Efficacy and Pharmacokinetic Equivalence to Full-length Recombinant Factor VIII. *Haemophilia* 2009; 1-12.
- Windyga J, Rusen L, Gruppo R, et al. BDDrFVIII (Moroctocog alfa [AF-CC]) for surgical haemostasis in patients with haemophilia A: results of a pivotal study. *Haemophilia.* 2010 Sep 1;16(5):731-9.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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. The drug product, diluents for injection and the rest of components included within the XYNTHA 250, 500, 1000, or 2000 International Units kit are free from natural rubber and natural rubber latex.

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

XYNTHA Vial Kit		
Nominal Strength	Fill Size Color Indicator	Vial Kit NDC #
250 International Units	Yellow	58394-012-01
500 International Units	Blue	58394-013-01
1000 International Units	Green	58394-014-01
2000 International Units	Red	58394-015-01

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.

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.

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

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.

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

How should I store XYNTHA?

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

Do not freeze.

Protect from light.

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

If stored at room temperature, XYNTHA can be returned 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

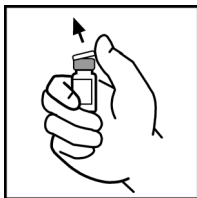
Preparation

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.

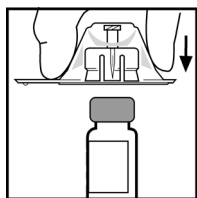
Reconstitution

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

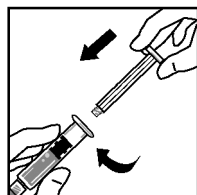
1. Let the XYNTHA vial and the prefilled diluent syringe reach room temperature.
2. Remove the plastic flip-top cap from the XYNTHA vial to show the center part of the rubber stopper.



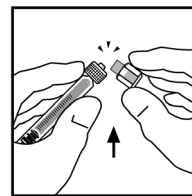
3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.
4. Peel back the cover from the clear plastic vial adapter package. **Do not remove the adapter 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.



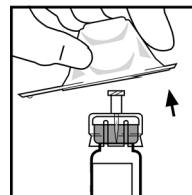
6. Grasp the plunger rod as shown in the picture below. Do not touch the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.



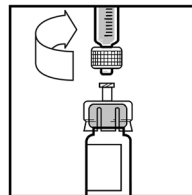
7. Break off the tamper-resistant, plastic tip cap from the diluent syringe by snapping the perforation of plastic of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if reconstituted XYNTHA is not used immediately), so place the cap on its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



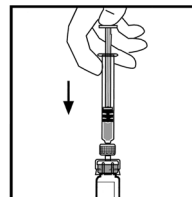
8. Lift the package cover away from the adapter and throw the package away.



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.

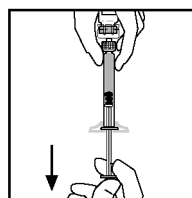


11. With the syringe still connected to the adapter, **gently** swirl the contents of the vial until the powder is dissolved.

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.



- 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

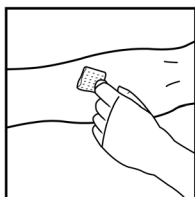
Your healthcare provider will teach you how to infuse XYNTHA yourself. Once you learn how to do this, you can follow the instructions in this insert.

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

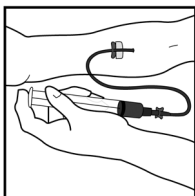
After reconstitution, be sure to look carefully at the XYNTHA solution. The solution should be clear to slightly opalescent and colorless. If it is not, throw away the solution and use a new kit.

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

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



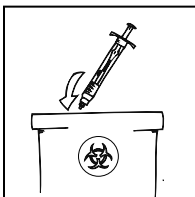
- Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein as instructed by your healthcare provider. Remove the tourniquet. Verify proper needle placement.
- Infuse the reconstituted XYNTHA product over several minutes. Your comfort level should determine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



- 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:

- Dispose of 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

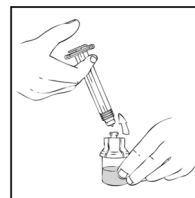
XYNTHA is also supplied in kits that have both the XYNTHA powder and the diluent within single-use prefilled dual-chamber syringes, called XYNTHA SOLOFUSE.

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.

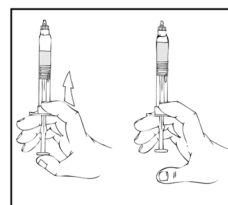
Use of a XYNTHA Vial Kit with a XYNTHA SOLOFUSE Kit

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.

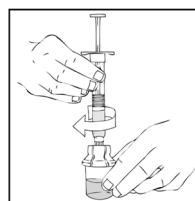
- Reconstitute the XYNTHA vial using the instructions described in **PREPARATION AND RECONSTITUTION OF XYNTHA** section. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the XYNTHA vial with the vial adapter in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



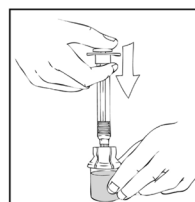
- Reconstitute the XYNTHA SOLOFUSE using the instructions included with the kit, remembering to remove most, but not all, of the air from the syringe.



- 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.

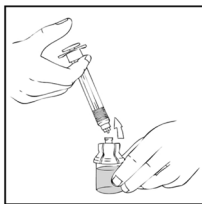


- Slowly depress the plunger rod of the XYNTHA SOLOFUSE until the contents empty into the XYNTHA vial. The plunger rod may move back slightly after release.

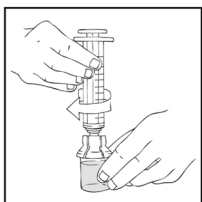


5. Detach the empty XYNTHA SOLOFUSE from the vial adapter and throw it away.

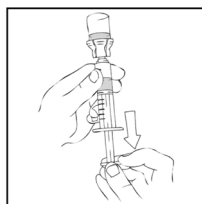
If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.



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.

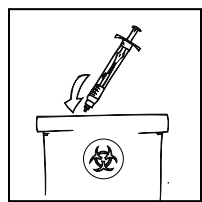


7. Invert the XYNTHA vial and slowly draw the solution into the large luer lock syringe.



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.



This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

Manufactured by



Wyeth Pharmaceuticals LLC

A subsidiary of Pfizer Inc, Philadelphia, PA 19101

License no: 3
LAB-0516-7.0

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XYNTHA® SOLOFUSE™ (antihemophilic factor [recombinant]) lyophilized powder for solution in prefilled dual-chamber syringe, for intravenous injection
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

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

DOSAGE 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. (2.1)
- Frequency of XYNTHA administration is determined by the type of bleeding episode and the recommendation of the treating physician. (2.1, 2.2)

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)

CONTRAINDICATIONS

Do not use in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster proteins. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

- The most common adverse reactions (≥10%) with XYNTHA in adult and pediatric previously treated patients (PTPs) were headache, arthralgia, pyrexia, and cough. (6)
- Across all studies, 4 subjects developed factor VIII inhibitors (2.4%). (6.2)

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

USE IN SPECIFIC POPULATIONS

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. (8.4)

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

Revised: 8/2019

FULL PRESCRIBING INFORMATION: CONTENTS *

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dose
 - 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 Kits
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Hypersensitivity Reactions
 - 5.2 Neutralizing Antibodies
 - 5.3 Monitoring Laboratory Tests
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
 - 6.2 Immunogenicity
 - 6.3 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

- On-demand treatment and control of bleeding episodes
- Perioperative management

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

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Titrate the administered doses to the patient's clinical response.
- One International Unit (IU) of factor VIII activity corresponds approximately to the quantity of factor VIII in one milliliter of normal human plasma. The calculation of the required dosage of factor VIII is based upon the empirical finding that, on average, 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by approximately 2 IU/dL.²

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

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

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

On-demand treatment and Control of Bleeding Episodes

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

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

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy
Minor Early hemarthrosis, minor muscle or oral bleeds.	20-40	12-24	At least 1 day, depending upon the severity of the bleeding episode.
Moderate Bleeding into muscles. Mild head trauma. Bleeding into the oral cavity.	30-60	12-24	3-4 days or until adequate local hemostasis is achieved.
Major Gastrointestinal bleeding, Intracranial, intra-abdominal, or intrathoracic bleeding. Fractures.	60-100	8-24	Until bleeding is resolved.

Perioperative Management

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

Table 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor Minor operations, including tooth extraction.	30-60	12-24	3-4 days or until adequate local hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major Major operations.	60-100	8-24	Until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved.

2.2 Preparation and Reconstitution

Preparation

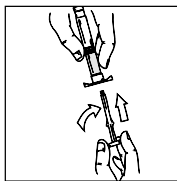
1. Always wash hands before performing the following procedures.
2. Use aseptic technique during the reconstitution procedures.
3. Use all components for the reconstitution and administration of this product as soon as possible after opening their sterile containers to minimize unnecessary exposure to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

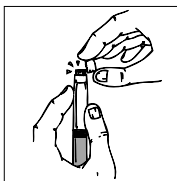
Reconstitution

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).

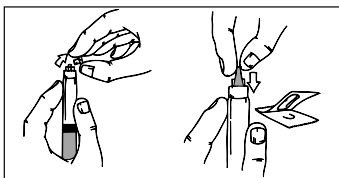


Note: Once the white tamper-evident seal is removed it is important to keep the XYNTHA SOLOFUSE in the upright position throughout the reconstitution process to prevent possible leakage.

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.

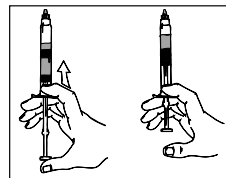


5. Remove the protective blue vented sterile cap from its package. While holding the XYNTHA SOLOFUSE upright, remove the grey rubber tip cap and replace it with the protective blue vented cap (prevents pressure build-up). Avoid touching the open end of both the syringe and the protective blue vented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

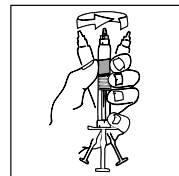


6. **Gently and slowly** advance the plunger rod by pushing until the two stoppers inside the XYNTHA SOLOFUSE meet, and all of the diluent is transferred to the chamber containing the XYNTHA powder.

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

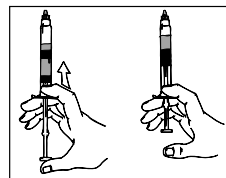


7. With the XYNTHA SOLOFUSE remaining upright, swirl **gently** several times until the powder is dissolved.



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.



Note:

- If the solution is not to be used immediately, store the syringe upright, leaving the protective blue vent cap on the XYNTHA SOLOFUSE until ready to infuse.
- Store the reconstituted solution at room temperature prior to administration, but use within 3 hours after reconstitution or after removal of the grey rubber tip cap.
- 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.**

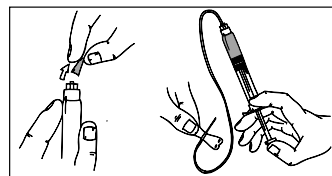
2.3 Administration

For intravenous infusion after reconstitution only.

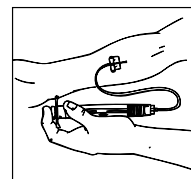
Inspect the final XYNTHA solution visually for particulate matter and discoloration prior to administration. The solution should be clear to slightly opalescent and colorless. If it is not, discard the solution and use a new kit.

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.



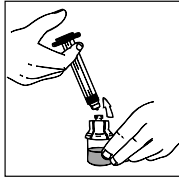
5. After infusing XYNTHA, remove and discard the infusion set. The amount of drug product left in the infusion set will not affect treatment.

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

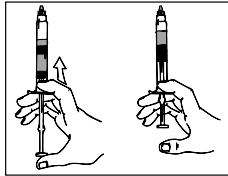
2.4 Use of a XYNTHA Vial Kit with a XYNTHA SOLOFUSE Kit

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.

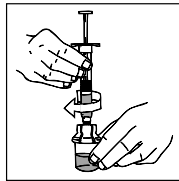
1. Reconstitute the XYNTHA vial using the instructions included with the product kit.
2. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the vial and the vial adapter in place.



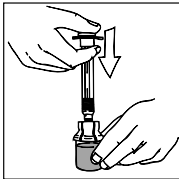
3. Reconstitute the XYNTHA SOLOFUSE using the instructions described in Preparation and Reconstitution [see Dosage and Administration (2.2)]. Remember to remove most, but not all, of the air from the drug product chamber.



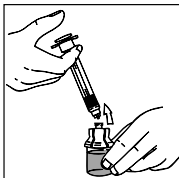
4. After removing the protective blue vented cap, connect the XYNTHA SOLOFUSE to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.



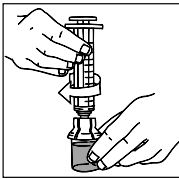
5. Slowly depress the plunger rod of the XYNTHA SOLOFUSE until the contents empty into the XYNTHA vial. The plunger rod may move back slightly after release.



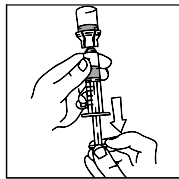
6. Detach and discard the empty XYNTHA SOLOFUSE from the vial adapter.
Note: If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.



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.



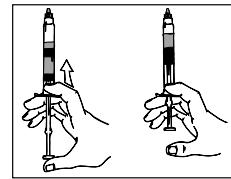
9. Detach the syringe from the vial adapter by gently turning and pulling the syringe counterclockwise. Discard the empty XYNTHA vial with the adapter attached.
10. Attach the infusion set to the large luer lock syringe as directed [see Dosage and Administration (2.3)].

2.5 Use of Multiple XYNTHA SOLOFUSE Kits

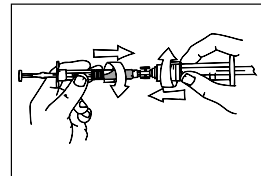
The instructions below are for the use of multiple XYNTHA SOLOFUSE kits with a 10 milliliter or larger luer lock syringe. For further information, please contact the Medical Information Department at Wyeth Pharmaceuticals, 1-800-438-1985.

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

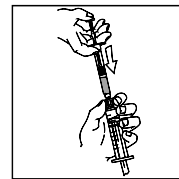
1. Reconstitute all XYNTHA SOLOFUSE according to instructions described in Preparation and Reconstitution [see Dosage and Administration (2.2)].
2. Holding the XYNTHA SOLOFUSE in an upright position, slowly advance the plunger rod until most, but not all, of the air is removed from the drug product chamber.



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 DOSAGE 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)].^{4,5,6,7,8,9,10,11,12}

5.3 Monitoring Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

XYNTHA was evaluated in five completed clinical studies (N=178), comprising four studies with adult and pediatric PTPs.

The safety and efficacy of XYNTHA was evaluated in two completed pivotal studies. In the first study (n=94), safety and efficacy were examined in PTPs with severe to moderately severe hemophilia A (factor VIII activity in plasma [FVIII:C] $\leq 2\%$) who received XYNTHA for routine prophylaxis and on-demand treatment. Ninety-four subjects received at least one dose of XYNTHA, resulting in a total of 6,775 infusions [see *Clinical Studies* (14)]. The second study (n=30) examined the use of XYNTHA for surgical prophylaxis in PTPs with severe to moderately severe hemophilia A (FVIII:C $\leq 2\%$) who required elective major surgery and were expected to receive XYNTHA replacement therapy for at least 6 days post-surgery. All subjects received at least one dose of XYNTHA, resulting in 1,161 infusions. One subject received XYNTHA for a pre-surgery pharmacokinetic assessment only and did not undergo surgery [see *Clinical Studies* (14)].

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

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

6.2 Immunogenicity

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

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

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

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

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

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

6.3 Postmarketing Experience

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

The following postmarketing adverse reaction has been reported for XYNTHA:

Inadequate therapeutic response

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

In the first completed open-label safety and efficacy study of XYNTHA (n=94), of the 18 adolescent subjects 12 to <17 years of age with severe to moderately severe hemophilia A (FVIII:C $\leq 2\%$), who were previously treated with at least 150 EDs to FVIII products, 10 subjects received XYNTHA for on-demand and follow-up treatment. The median dose per on-demand infusion was 47 IU/kg (min-max: 24-74) and the median exposure per subject was 6 days (min-max: 1-26).

Of the 18 subjects <17 years of age who received at least 1 dose of XYNTHA, 10 subjects had bleeding episodes during the study. A total of 66 bleeding episodes were treated with on-demand infusions of XYNTHA. The majority of the bleeding episodes (63/66 or 95%) resolved with 1 or 2 infusions. The response to infusion was rated on a pre-specified 4 point hemostatic efficacy scale. Thirty-eight (38) of 66 bleeding episodes (58%) were rated excellent or good in their response to initial treatment, 24 (36%) were rated as moderate, and 4 (6%) were not rated.

Additional data for 50 subjects are available from a second safety and efficacy study of XYNTHA in children <16 years of age with severe to moderately severe hemophilia A (FVIII:C $\leq 2\%$) and with at least 20 prior EDs to FVIII products. Of the 50 subjects, 38 subjects received XYNTHA for on-demand and follow-up treatment of bleeding episodes. The median dose per on-demand infusion was 28 IU/kg (min-max: 10-92) and the median exposure per subject was 9 days (min-max: 1-95).

Of the 50 subjects <16 years of age who received at least 1 dose of XYNTHA, 38 had 562 bleeding episodes during the study. The majority of the bleeding episodes (518/562 or 92%) resolved with 1 or 2 infusions. Of 559 bleeding episodes treated with XYNTHA with response assessments to the first infusion, 526 (94%) were rated excellent or good in their response to initial treatment and 27 (5%) were rated as moderate.

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

11 DESCRIPTION

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

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

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

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

XYNTHA is formulated as a sterile, nonpyrogenic, no preservative, lyophilized powder preparation for intravenous injection. Each single-use prefilled dual-chamber syringe

(named XYNTHA SOLOFUSE) contains nominally 250, 500, 1000, 2000, or 3000 IU of XYNTHA. Upon reconstitution, the product is a clear to slightly opalescent, colorless solution that contains sodium chloride, sucrose, L-histidine, calcium chloride and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

Parameter	Initial Visit (n = 30)	Month 6 (n = 25)	Pre-surgery (n=8)
C _{max} (IU/mL)	1.08 ± 0.22	1.24 ± 0.42	1.08 ± 0.24
AUC _∞ (IU·hr/mL)	13.5 ± 5.6	15.0 ± 7.5	16.0 ± 5.2
t _{1/2} (hr)	11.2 ± 5.0	11.8 ± 6.2*	16.7 ± 5.4
CL (mL/hr/kg)	4.51 ± 2.23	4.04 ± 1.87	3.48 ± 1.25
V _{ss} (mL/kg)	66.1 ± 33.0	67.4 ± 32.6	69.0 ± 20.1
Recovery (IU/dL per IU/kg)	2.15 ± 0.44	2.47 ± 0.84	2.17 ± 0.47

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

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

Table 4 shows the pharmacokinetic parameters of nine children; four aged 14 or 15 years of age, who are also included in the summary for the adults above, along with five children aged 3.7-5.8 years after single 50 IU/kg doses of XYNTHA. Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximately 40% higher in children.

Parameter	Young Children (n=5)	Adolescents (n=4)
Age (min - max, yr)	3.7 - 5.8	14 - 15
C _{max} (IU/mL)	0.78 ± 0.34	0.97 ± 0.21
AUC _∞ (IU·hr/mL)	12.2 ± 6.50	8.5 ± 4.0
t _{1/2} (hr)	8.3 ± 2.7	6.9 ± 2.4
CL (mL/hr/kg)	6.29 ± 4.87	6.62 ± 2.16
V _{ss} (mL/kg)	66.9 ± 55.6	67.1 ± 13.6
Recovery (IU/dL per IU/kg)	1.52 ± 0.69	1.95 ± 0.41

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

Preclinical studies evaluating XYNTHA in hemophilia A dogs without inhibitors demonstrated safe and effective restoration of hemostasis. XYNTHA demonstrated a toxicological profile that was similar to the toxicological profile observed with the predecessor product. Toxicity associated with XYNTHA was primarily associated with

anti-FVIII neutralizing antibody generation first detectable at 15 days of repeat dosing in high (approximately 735 IU/kg/day) level-dosed, non-human primates.

14 CLINICAL STUDIES

Two completed multicenter, open-label studies support the analysis of safety and efficacy of XYNTHA in on-demand treatment and control of bleeding episodes and perioperative management. These completed clinical studies for XYNTHA examined 124 PTP subjects, 94 for on-demand treatment and routine prophylaxis and 30 for surgical prophylaxis. Subjects with severe to moderately severe hemophilia A (FVIII:C ≤2%) and no history of FVIII inhibitors were eligible for the trials.

On-demand treatment and Control of Bleeding Episodes

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

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

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, min-max: 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%) occurred ≤48 hours after the last dose and 39% (70/180 bleeds) occurred >48 hours after the last dose. The majority of bleeds reported to occur ≤48 hours after the last prophylaxis dose were traumatic (64/110 bleeds or 58%). Forty-two bleeds (42/70 or 60%) reported to occur >48 hours after the last prophylaxis dose were spontaneous. The on-demand treatment dosing regimen was determined by the investigator. The median dose for on-demand treatment was 31 IU/kg (min-max: 6-74 IU/kg) and the median exposure per subject was 3 days (min-max: 1-26).

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

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

^a *Excellent*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered.

^b *Good*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.

^c *Moderate*: Probable or slight improvement starting after 8 hours following the infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.

^d *No Response*: No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens.

^e Includes one infusion with commercial FVIII that occurred before routine prophylaxis began.

Perioperative Management

In a study (n=30) for surgical prophylaxis in subjects with hemophilia A, XYNTHA was administered to 25 efficacy-evaluable PTPs undergoing major surgical procedures (11 total knee replacements, 1 hip replacement, 5 synovectomies, 1 left ulnar nerve transposition release, 1 ventral hernia repair/scar revision, 1 knee arthroscopy, 1 revision and debridement of the knee after a total knee replacement, 1 hip arthroplasty revision, 1 stapes replacement, 1 ankle arthrodesis, and 1 pseudotumor excision).¹⁷

The results of the hemostatic efficacy ratings for these subjects are presented in Table 6. Investigator's ratings of efficacy at the end of surgery and at the end of the initial post-operative period were excellent or good for all assessments. Intraoperative blood loss was reported as "normal" or "absent" for all subjects. Thirteen of the subjects (13/25 or 52%) had blood loss in the postoperative period. The postoperative blood loss was rated as "normal" for ten of these cases while three cases were rated "abnormal" (1 due to

hemorrhage following surgical trauma to the epigastric artery, 1 due to an 800 mL blood loss after hip replacement surgery, and 1 after an elbow synovectomy where the blood loss could not be measured by the investigator).

Table 6: Summary of Hemostatic Efficacy

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

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

15 REFERENCES

- Nilsson IM, Berntorp EE and Freiburghaus C. Treatment of patients with factor VIII and IX inhibitors. *Thromb Haemost.* 1993;70(1):56-59.
- Hoyer LW. Hemophilia A. *N Engl J Med.* 1994;330:38-47.
- Juhlin F. Stability and Compatibility of Reconstituted Recombinant Factor VIII SQ, 250 IU/ml, in a System for Continuous Infusion. Pharmacia Document 9610224, 1996.
- Ehrenforth S, Kreuz W, Scharrer I, et al. Incidence of development of factor VIII and factor IX inhibitors in hemophiliacs. *Lancet.* 1992;339:594-598.
- Lusher J, Arkin S, Abildgaard CF, Schwartz RS, the Kogenate PUP Study Group. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. *N Engl J Med.* 1993;328:453-459.
- Bray GL, Gomperts ED, Courter S, et al. A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. *Blood.* 1994;83(9):2428-2435.
- Kessler C, Sachse K. Factor VIII:C inhibitor associated with monoclonal-antibody purified FVIII concentrate. *Lancet.* 1990;335:1403.
- Schwartz RS, Abildgaard CF, Aledort LM, et al. Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. *N Engl J Med.* 1990;323:1800-1805.
- White GC II, Courter S, Bray GL, et al. A multicenter study of recombinant factor VIII (Recombinate™) in previously treated patients with hemophilia A. *Thromb Haemost.* 1997;77(4):660-667.
- Gruppo R, Chen H, Schroth P, et al. Safety and immunogenicity of recombinant factor VIII (Recombinate™) in previously untreated patients: A 7.3 year update. *Haemophilia.* 1998;4:228 (Abstract No. 291, XXIII Congress of the WFH, The Hague).
- Scharrer I, Bray GL, Neutzling O. Incidence of inhibitors in haemophilia A patients - a review of recent studies of recombinant and plasma-derived factor VIII concentrates. *Haemophilia.* 1999;5:145-154.
- Abshire TC, Brackmann HH, Scharrer I, et al. Sucrose formulated recombinant human antihemophilic Factor VIII is safe and efficacious for treatment of hemophilia A in home therapy: Results of a multicenter, international, clinical investigation. *Thromb Haemost.* 2000;83(6):811-816.
- Sandberg H, Almstedt A, Brandt J, Castro VM, Gray E, Holmquist L, et al. Structural and Functional Characterization of B-Domain Deleted Recombinant Factor VIII. *Sem Hematol.* 2001;38 (Suppl. 4):4-12.
- Kelley BD, Tannatt M, Magnusson R, Hagelberg S. Development and Validation of an Affinity Chromatography Step Using a Peptide Ligand for cGMP Production of Factor VIII. *Biotechnol Bioeng.* 2004;87(3):400-412.
- Mann KG and Ziedens KB. Overview of Hemostasis. In: Lee CA, Berntorp EE and Hoots WK, eds. *Textbook of Hemophilia.* USA, Blackwell Publishing; 2005:1-4.
- Recht M, Nemes L, Matysiak M et al. Clinical Evaluation of Moroctocog Alfa (AF-CC), a New Generation of B-Domain Deleted Recombinant Factor VIII (BDDrFVIII) for Treatment of Haemophilia A: Demonstration of Safety, Efficacy and Pharmacokinetic Equivalence to Full-length Recombinant Factor VIII. *Haemophilia* 2009; 1-12.
- Windyga J, Rusen L, Gruppo R, et al. BDDrFVIII (Moroctocog alfa [AF-CC]) for surgical haemostasis in patients with haemophilia A: results of a pivotal study. *Haemophilia.* 2010 Sep 1;16(5):731-9.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Each XYNTHA SOLOFUSE Kit contains: one plunger rod for assembly, one sterile infusion set, two alcohol swabs, one bandage, one gauze pad, one vented sterile cap, and one package insert. The drug product, diluents for injection and the rest of components included within the XYNTHA 250, 500, 1000, 2000, or 3000 International Units kit are free from natural rubber and natural rubber latex.

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:

XYNTHA SOLOFUSE Kit		
Nominal Strength	Fill Size Color Indicator	Kit NDC #
250 International Units	Yellow	58394-022-03
500 International Units	Blue	58394-023-03
1000 International Units	Green	58394-024-03
2000 International Units	Red	58394-025-03
3000 International Units	Gray	58394-016-03

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

Storage and Handling

Product as Packaged for Sale:

- Store XYNTHA SOLOFUSE 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 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. 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.

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.

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

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. 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

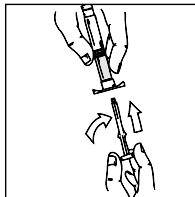
Preparation

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.

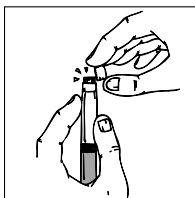
Reconstitution

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).

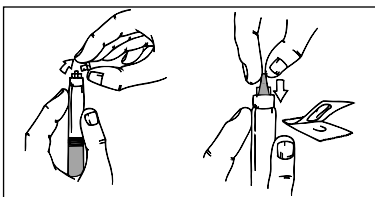
Throughout the reconstitution process, it is important to keep the XYNTHA SOLOFUSE upright to prevent possible leakage.



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.

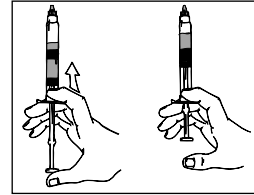


5. Remove the protective blue vented sterile cap from its package. While holding the XYNTHA SOLOFUSE upright, remove the grey rubber tip cap and replace it with the protective blue vented cap (prevents pressure build-up). Avoid touching the open end of both the syringe and the protective blue vented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

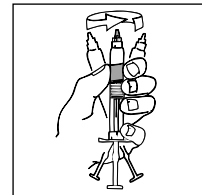


6. **Gently and slowly** push the plunger rod until the two stoppers inside the XYNTHA SOLOFUSE meet, and all of the diluent is transferred to the chamber containing the XYNTHA powder.

Note: To prevent the escape of fluid from the tip of the syringe, do not push the plunger rod with excessive force.

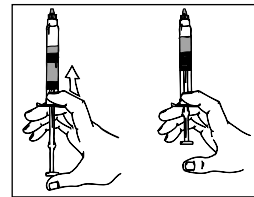


7. With the XYNTHA SOLOFUSE remaining upright, swirl **gently** several times until the powder is dissolved.



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

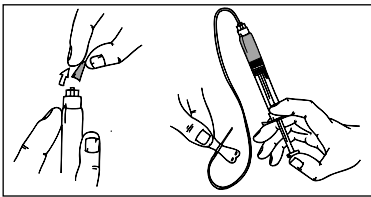
Your healthcare provider will teach you how to infuse XYNTHA yourself. Once you learn how to do this, you can follow the instructions in this insert.

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

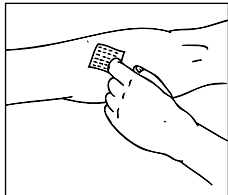
After reconstitution, be sure to look carefully at the XYNTHA solution. The solution should be clear to slightly opalescent and colorless. If it is not, throw away the solution and use a new kit.

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

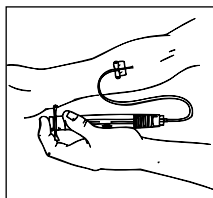
1. After removing the protective blue vented cap, firmly attach the intravenous infusion set provided in the kit onto the XYNTHA SOLOFUSE.



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



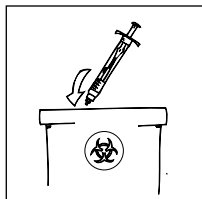
3. Remove the protective needle cover and insert the butterfly needle of the infusion set tubing into your vein as instructed by your healthcare provider. Remove the tourniquet. Verify proper needle placement.
4. Infuse the reconstituted XYNTHA product over several minutes. Your comfort level should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

- Dispose of 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.

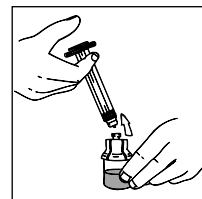
If you use one XYNTHA vial and one XYNTHA SOLOFUSE for the infusion, reconstitute the XYNTHA vial and the XYNTHA SOLOFUSE according to the specific directions for that respective product kit. Use a separate, 10 milliliter or larger luer lock syringe (not included in this kit) to draw back the reconstituted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

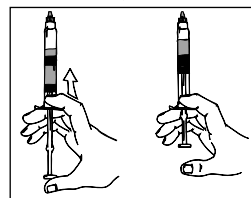
Use of a XYNTHA Vial Kit with a XYNTHA SOLOFUSE Kit

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.

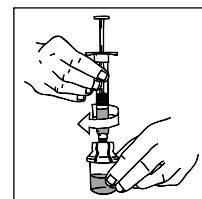
1. Reconstitute the XYNTHA vial using the instructions included with the kit. Detach the empty diluent syringe from the vial adapter by gently turning and pulling the syringe counterclockwise, leaving the contents in the XYNTHA vial with the vial adapter in place.



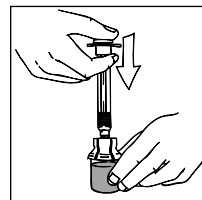
2. Reconstitute the XYNTHA SOLOFUSE using the instructions included with the product kit, remembering to remove most, but not all, of the air from the syringe.



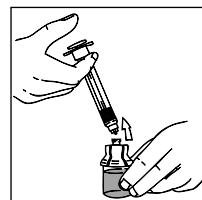
3. After removing the protective blue vented cap, connect the XYNTHA SOLOFUSE to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.



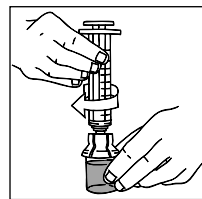
4. Slowly push the plunger rod of the XYNTHA SOLOFUSE to empty the contents into the XYNTHA vial. The plunger rod may move back slightly after release.



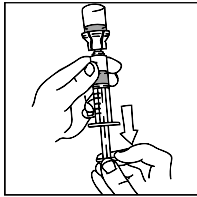
5. Detach the empty XYNTHA SOLOFUSE from the vial adapter and throw it away. If the syringe turns without detaching from the vial adapter, grasp the white collar and turn.



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.

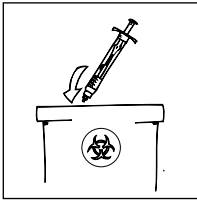


7. Invert the XYNTHA vial and slowly draw the solution into the large luer lock syringe.



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.

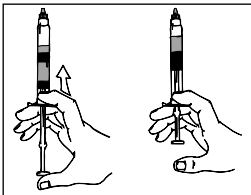


Use of Multiple XYNTHA SOLOFUSE Kits

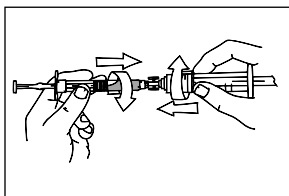
The instructions below are for the use of multiple XYNTHA SOLOFUSE kits with a 10 milliliter or larger luer lock syringe. For further information, please contact your healthcare provider or call the Medical Information Department at Wyeth Pharmaceuticals, 1-800-438-1985.

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

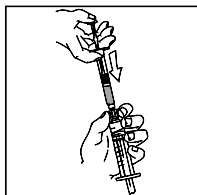
1. Reconstitute all XYNTHA SOLOFUSE according to instructions described in **PREPARATION AND RECONSTITUTION OF XYNTHA SOLOFUSE** section. Holding the XYNTHA SOLOFUSE in an upright position, slowly push the plunger rod until most, but not all, of the air is removed from the syringe.



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.

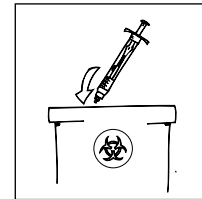


4. With the XYNTHA SOLOFUSE on top, slowly push the plunger rod to empty all the XYNTHA SOLOFUSE content into the large luer lock syringe.



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.



This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

Manufactured by



Wyeth Pharmaceuticals LLC

A subsidiary of Pfizer Inc, Philadelphia, PA 19101

License no: 3

LAB-0500-11.0