Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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From:	Meghna Alimchandani, MD Deputy Director, Division of Pharmacovigilance (DPV), OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Wyeth Pharmaceuticals, LLC
Product:	Xyntha (Antihemophilic Factor (Recombinant), Plasma/Albumin Free)
STN:	125264/1939
Indication:	Xyntha is a recombinant antihemophilic factor indicated in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, for perioperative management, and for routine prophylaxis to reduce the frequency of bleeding episodes. Xyntha is not indicated in patients with von Willebrand's disease.
Meeting Date:	Pediatric Advisory Committee Meeting, 2024

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1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of the supplemental Biologics License Application (sBLA 125264/1670), on August 13, 2020, for routine prophylaxis to reduce the frequency of bleeding episodes in children and adults with hemophilia A.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

Xyntha is a recombinant antihemophilic factor indicated in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, for perioperative management, and for routine prophylaxis to reduce the frequency of bleeding episodes. Xyntha is not indicated in patients with von Willebrand's disease.

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 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. Xyntha is formulated as a sterile, nonpyrogenic, no preservative, lyophilized powder preparation for intravenous injection. It is supplied in a kit that includes the Xyntha lyophilized powder containing nominally 250, 500, 1000, 2000, or 3000 IU of Xyntha and 4 mL 0.9% sodium chloride solution for reconstitution in a single-use prefilled dual-chamber syringe.

1.3 Regulatory History

- February 21, 2008: Initial FDA approval of BLA 125264/0 for control and prevention of bleeding episodes and for surgical prophylaxis in patients with hemophilia A.
- October 17, 2014: FDA approval of sBLA 125264/1396 to include expansion of the indication for Xyntha to include all pediatric age groups.
- August 13, 2020: FDA approval of sBLA 125264/1670 for routine prophylaxis to reduce the frequency of bleeding episodes in children and adults with hemophilia A. Note that the sponsor fulfilled the pediatric study requirement for all relevant pediatric age groups under Pediatric Research Equity Act (PREA) with this submission.
    - Regulatory trigger for current PAC review, subject of this memorandum

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS) reports for Xyntha during August 13, 2020, to October 31, 2023 (safety review period)
- Manufacturer's submissions
    - Xyntha U.S. package insert; Revised: 7/2022
    - Applicant response to information request regarding dose distribution data, received December 4, 2023
    - U.S. Pharmacovigilance Plan dated December 14, 2007 (Version 2)
    - Periodic safety reports
- FDA Documents
    - Xyntha sBLA 125264/1670 approval letter
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety related labeling changes during August 13, 2020, to October 31, 2023.

4 PRODUCT UTILIZATION DATA

Wyeth provided the following estimates of Xyntha distribution data and patient exposure data for the U.S. and worldwide for the safety review period.

- U.S. distribution data for Xyntha during August 13, 2020, to October 31, 2023: 188,342 sales units, and estimated U.S. patient exposure was 1,207 patient-years
- Worldwide distribution data for Xyntha during August 13, 2020, to October 31, 2023: 2,069,655 sales units, and estimated worldwide patient exposure was 13,267 patient-years

Additional breakdown of U.S. patient exposure by age (pediatric v. adults) was not available. These data were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The current Pharmacovigilance Plan (PVP) for Xyntha is dated December 14, 2007 (Version 2) and lists the following important identified and potential risks, and missing information (see Table 1).

Table 1: Xyntha Safety Concerns

Important Identified Risks
Inhibitor Development
Less Than Expected Therapeutic Effect
Allergic Type Hypersensitivity Reaction
Important Potential Risks
Potential for Medication Errors/Product Confusion Risks^
Missing Information
Pediatric Treatment in children under age 12^
Previously Untreated Patients (PUPs) Treatment
Subjects with previous history of inhibitor formation

^As per sponsor communications received on January 26, 2024, and February 7, 2024, in response to FDA information requests, the sponsor confirmed that:
(1) the inclusion of "Potential for Medication Errors/Product Confusion Risks" as an important potential risk "stems from the introduction of Xyntha to the US market in 2008 and the simultaneous existence of two versions of moroctocog alpha (Xyntha and ReFacto) in the United States market at that time." Subsequently, ReFacto was discontinued on May 2, 2017, and there are no lots of ReFacto within expiration in the U.S. The risk of product confusion is no longer applicable in the U.S. given that Xyntha is the only currently available product in the U.S. and
(2) data regarding the use of Xyntha in subjects younger than 12 years of age is no longer considered missing information as it is included in Section 8.4 *Pediatric* Use of the USPI, which states, "Safety and efficacy with Xyntha were evaluated in clinical studies in 68 pediatric subjects <17 years of age (18 subjects aged 12 to <17 years, 50 subjects aged ≤12 years). There were no apparent differences in the efficacy and safety in pediatric subjects as compared to adults."

The important identified risks for Xyntha are labeled events and consistent with the safety profile of other factor VIII products. Development of neutralizing antibodies is described in Warnings and Precautions and Adverse Reactions sections of the USPI. The Warnings and Precautions Section of the USPI includes a statement on "Monitoring Laboratory Tests" with instructions to monitor plasma factor VIII activity levels and monitor for development of inhibitors. Inadequate therapeutic response is labeled under Postmarketing Experience section of USPI. Hypersensitivity reactions are also labeled under Warnings and Precautions of the USPI.

The important identified and potential risks listed in Table 1 are monitored with routine pharmacovigilance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement or commitment (PMR/PMC) safety studies or a Risk Evaluation and Mitigation Strategy (REMS) for Xyntha.

5.2 Postmarketing Studies

Postmarketing requirement under Pediatric Research Equity Act (PREA): Submission for sBLA 125264/1670 for routine prophylaxis to reduce the frequency of bleeding episodes in children and adults with hemophilia A triggered PREA and fulfilled the

PREA postmarketing requirements (PMRs). The approval of this sBLA is the trigger for the PAC review that is the subject of this memorandum.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Xyntha between August 13, 2020 (approval of sBLA 125264/1670 and trigger for this PAC review) to October 31, 2023 (data lock point). FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of AE reports for Xyntha during the safety review period are listed in Table 2 below. There were 110 reports, including 72 U.S. and 38 foreign reports for the safety review period August 13, 2020 to October 31, 2023.

Table 2: Xyntha FAERS reports during review period (August 13, 2020 – October 31, 2023)

Age	Serious Non-Fatal*		Deaths		Non-Serious		Total Reported	
	US	Foreign	US	Foreign^	US	Foreign	US	Foreign
<17 years	1	2	0	1	1	0	2	3
≥ 17 years	39	10	3	12	13	0	55	22
Unknown	8	7	2	1	5	5	15	13
All Ages	48	19	5	14	19	5	72	38

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).
^Query initially retrieved 13 foreign death reports with age unspecified; in many cases, review of narratives described patients as adults or pediatric, and the case counts in this table were updated.

6.2.1 Deaths

There were 19 deaths (14 foreign, 5 U.S.) reported during the safety review period August 13, 2020, to October 31, 2023, of which there was one pediatric death. The pediatric death involved a case of cerebral hemorrhage with minimal clinical details; this report was part of a cluster of 6 foreign reports of cerebral hemorrhage (discussed below).

Foreign reports (n = 14): There were 6 reports of cerebral hemorrhage in male patients: one case involved a pediatric patient, 4 cases involved adult patients and age was unknown for one case. There were 2 reports of myocardial infarction in adult patients. There were single reports for the following AEs with fatal outcomes involving adult patients: malignant neoplasm, infection, gastrointestinal hemorrhage, gastric hemorrhage. One "elderly male patient" was reported to have died "from natural causes." Cause of death was unknown for a 62-year-old male patient.

U.S. reports (n = 5): There were 2 reports of accidents with fatal outcomes. Cause of death was unknown for an 80-year-old female patient. The remaining death reports involved a 58-year-old male patient with laryngeal squamous cell carcinoma and a female patient of unknown age with unspecified malignant neoplasm.

Reviewer comments: Most death reports contained minimal case details. Several patients had bleeding events and other diagnoses that may have contributed to the fatal episodes. Review of the death reports did not identify any new safety concerns.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 67 serious non-fatal reports, including 3 pediatric reports and 49 adult reports. Age was unknown for the remaining 15 reports.

Pediatric serious non-fatal reports included the following:

- Appendicitis in a 9-year-old female patient
- 14-year-old male patient sustained left elbow fracture
- Literature case report describing 11-year-old male patient treated with Xyntha and multiple factor products, who developed inhibitors and experienced allergic reaction and respiratory compromise.[1]

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for adult and pediatric serious reports are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs for non-fatal serious reports

Preferred Term (PT)	**# Reports**	**Label status for AE** *Xyntha U.S. package insert; Revised: 7/2022*	**Reviewer comments**
Hemorrhage	34	Unlabeled	Confounded by indication (Bleeding episodes described in section 14 of USPI)

[1] Liu G, Chen Z, Wu W, Wu R. Development and desensitization therapy of high-response factor VIII inhibitors with severe allergic reaction in a moderate hemophilia A patient. Int J Immunopathol Pharmacol. 2021 Jan-Dec;35:2058738420980259. doi: 10.1177/2058738420980259. PMID: 33626954; PMCID: PMC7917874.

Preferred Term (PT)	# Reports	Label status for AE *Xyntha U.S. package insert; Revised: 7/2022*	Reviewer comments
Hemarthrosis	6	Unlabeled	Confounded by indication (Bleeding episodes described in section 14 of USPI)
Off label use	3	Not applicable	Does not represent an AE
Pain	3	Unlabeled	Arthralgia is labeled in section 6.1 Clinical Trials Experience of USPI
Poor venous access	3	Not applicable	Does not represent an AE

Note: PTs occurring with a frequency > 2 reports are shown in above table.

Reviewer comments: Hemorrhage and hemarthrosis represent bleeding events associated with underlying hemophilia. Pain is a non-specific AE and may be related to the labeled AE for arthralgia. There were no new safety concerns.

6.2.3 Non-serious Reports

During the reporting period, there were 24 non-serious reports; including 13 adult reports, one pediatric report, and age was unknown for the remaining 10 reports. The top PTs for non-serious reports include *Device leakage* and *Off label use.* No other PTs appeared in more than 2 reports. The single pediatric report involved a 7-year-old male patient who sustained a knee injury.

Reviewer comments: There were 5 non-serious reports with PT for device leakage describing occurrence of leakage from the portion of the product where the plunger attaches to the syringe or leakage from the vial after reconstitution; these reports were not associated with clinical AEs. In three of the reports, the product was discarded, in one report the patient was reported to have received an underdose due to product leakage, and in the remaining report it is unclear if the patient used the product. These complaints were investigated by the sponsor, and the investigation included reviewing batch records, remaining samples if available, deviation investigations and analysis of the complaint history for the reported lot. The sponsor investigation concluded that there were no deviations related to product quality; the review of historical data showed no potential trend; and additional corrective or preventive actions were not identified. Of note, the USPI, section 2.2. *Preparation and Reconstitution*, includes instructions and figures describing preparation, reconstitution and administration using the kit, and the components of the kit are described in section 16 *How Supplied/Storage and Handling* of the USPI. Overall, there were few non-serious reports during the safety review period, and no new safety concerns were identified.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Xyntha were disproportionally reported compared to all products in the FAERS database. Data

mining covers the entire postmarketing period for this product, from initial licensure through the data lock point as of December 3, 2023. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product Name (S) run identified the PTs summarized below with a disproportional reporting alert. Note that a report may have one or more PTs. (Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

> PTs representing bleeding episodes and confounded by indication and related to underlying hemophilia: Hemorrhage; Hemarthrosis; Joint injury*; Joint swelling*; Arthropathy; Hemophilic arthropathy; Hematoma; Cerebral haemorrhage; Contusion; Muscle haemorrhage; Mouth hemorrhage.
> *Of note, Arthralgia is labeled in 6.1 Clinical Trials Experience.
>
> Labeled PT: Factor VIII inhibition (Labeled under Warnings and Precautions)
>
> Non-specific PTs that may also represent confounding by indication (i.e., events leading to on-demand treatment): Fall; Disease complication, Limb injury, Injury, Tooth disorder.
>
> Non-specific PTs that do not represent a clinical AE: Road traffic accident, Accident, Device leakage; Syringe issue; Poor venous access.

Reviewer comments: Most of these events appeared among the most frequently reported PTs and are discussed in Section 6.2. Factor VIII inhibition is a labeled complication of all factor VIII products. The remaining PTs describe bleeding events and are associated with underlying hemophilia disease, which is a chronic disorder of coagulation that results in episodes of bleeding. Alternatively these are descriptions of product ineffectiveness or indicate the development of inhibitors in these patients such that the Factor VIII is not effective in stopping the bleeding.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Xyntha were reviewed. The AEs reported were consistent with those seen in FAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on December 11, 2023 for peer-reviewed literature, with the search term "Xyntha" and "safety" limited by human species, and dates from PAC trigger (August 13, 2020) to date of search December 11, 2023, retrieved one publication pertaining to safety. No new safety

concerns for Xyntha were identified in the review of this publication, summarized in the table below.

Publication	Authors' Safety Conclusion
Xi Y, Jin C, Liu W, Zhou H, Wang Z, Zhou R, Lou S, Zhao X, Chen F, Cheng P, Sun Z, Jia H, Zhang L. Efficacy, safety and bioequivalence of the human-derived B-domain-deleted recombinant factor VIII TQG202 for prophylaxis in severe haemophilia A patients. Haemophilia. 2022 Nov;28(6):e219-e227. doi: 10.1111/hae.14652. Epub 2022 Aug 22. PMID: 35996199; PMCID: PMC9805152.	A multicenter, randomized, open-label clinical trial was conducted to evaluate the efficacy and safety of a new B-domain deleted (BDD) recombinant FVIII (TQG202) for prophylaxis in severe hemophilia A patients to compare the bioequivalence with Xyntha. Results demonstrated that TQG202 showed bioequivalence with Xyntha. No participants developed FVIII inhibitors. There were no new safety concerns.

8 CONCLUSION

This postmarketing pediatric safety review for Xyntha was triggered by the approval of the sBLA 125264/1670, on August 13, 2020, for routine prophylaxis to reduce the frequency of bleeding episodes in children and adults with hemophilia A.
Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and published literature does not indicate any new safety concerns. Overall, there were few pediatric reports. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label or confounded by indication. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Xyntha.