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 Epidemiology (DE), OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Grifols
Product:	Xembify [(immune globulin subcutaneous, human – klhw)]
STN:	125683/167
Indication:	Treatment of Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older.
Meeting Date:	Pediatric Advisory Committee Meeting, April 2022

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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 is the July 3, 2019 approval of Xembify for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older.

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

1.2 Product Description

Xembify (immune globulin subcutaneous, human – klhw) is a 20% immune globulin solution for subcutaneous injection indicated for treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older. Xembify is a 20% ready-to-use sterile, non-pyrogenic human immune globulin solution made from large pools of human plasma. The manufacturing process is similar to that of Grifols' 10% immune globulin intravenous product, Gamunex-C. Xembify is presented in liquid form, in single-use glass vials.

1.3 Regulatory History

FDA approved Xembify as an original Biologics License Approval (BLA 125683/0) on July 3, 2019 for the treatment of PI in patients ≥ 2 years (t*rigger for the PAC).*

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Xembify during July 3, 2019 to October 22, 2021
- Manufacturer's Submissions
    - Xembify, U.S. package insert (USPI), updated December 29, 2020
    - Applicant response to information request regarding dose distribution data
    - Pharmacovigilance plan, version 1.0, dated July 6, 2018
    - Periodic safety reports
- FDA Documents
    - BLA 125683/0 Xembify Approval Letter, dated July 3, 2019
    - BLA 125683/0 OBE/DE Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

4 PRODUCT UTILIZATION DATA[1]

During July 3, 2019 to October 22, 2021, there were (b) (4) of Xembify sold in the U.S. Grifols estimates the percentage of use in the pediatric population to be (b) (4) for the approved indication for treatment of PI.

Dosage for this subcutaneous immune globulin product is guided by the patient's serum IgG trough level. The dose is individualized based on the patient's pharmacokinetic and clinical response.

(b) (4) during the review period.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan (PVP), version 1.0, dated July 6, 2018, lists the important identified risks, important potential risks, and missing information displayed in Table 1.

Table 1: Xembify safety concerns

Important Identified Risks
• Infusion site reaction
Important Potential Risks
• Hypersensitivity reactions including anaphylactic reactions • Thromboembolic events • Aseptic meningitis • Theoretical risk of pathogen infection • Interaction with live attenuated vaccines
Missing Information
• Use in women who are pregnant or lactating • Use in geriatric population.

The identified and potential risks for Xembify listed in the above table are common to the immune globulin product class, and most of these risks are described in the USPI. In clinical trials, the most common adverse reactions were local adverse reactions including infusion site reaction. Xembify has a boxed warning for thrombosis. The USPI includes warnings for thrombosis, hypersensitivity, aseptic meningitis syndrome, transmissible infectious agents and interference with laboratory tests.

[1] Distribution data is protected as confidential commercial information and may require redaction from this review.

Thrombotic events: Prior to this PAC trigger, in 2013, a boxed warning[2] for thrombosis was added to the label of all non-specific immune globulin products, as required by FDA. As per FDA safety communication, "A retrospective analysis of data from a large health claims-related database, as well as continued postmarketing adverse event reports of thrombosis, have strengthened the evidence for an association between the use of intravenous, subcutaneous, and intramuscular human immune globulin products and the risk of thrombosis. This information necessitates a boxed warning for the entire class of products."[3] The risk of thrombosis was identified prior to the approval for Xembify, and it is considered applicable to all immune globulin products and labeled for this entire product class.

The identified and potential risks for Xembify are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no ongoing or planned additional pharmacovigilance activities for Xembify, such as postmarketing safety studies or Risk Evaluation and Mitigation Strategy (REMS).

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Xembify received between July 3, 2019 (PAC trigger) to October 22, 2021 (data lock point for this review period). 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.

[2] FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. November 7, 2013. Available at: https://www.gmp-compliance.org/gmp-news/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products

[3] FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. June 11, 2013. Available at: https://primaryimmune.org/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products

6.2 Results

The results of the FAERS search of adverse event reports for Xembify during the review period are listed in Table 2. There were 47 U.S. reports. There were no foreign reports.

Table 2: FAERS reports for Xembify (July 3, 2019 to October 22, 2021)

Age (years)	Serious non-fatal, US	Deaths, US	Non-Serious, US	Total, US
<18	0	0	3	3
≥18	7	0	15	22
Unknown	1	0	21	22
All	8	0	39	47

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).

6.2.1 Deaths

There were no death reports.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 8 serious non-fatal reports, none of which involved a pediatric patient.
The most frequently reported adverse event Preferred Terms (PTs) occurring in >1 serious report are shown in the table below. Note that a report may have one or more PTs.

Table 3: Top PTs for serious reports

Preferred Term (PT)	Number of reports	Label status
Headache	2	*Severe headache* is labeled under Warnings and Precautions, section 5.3 Aseptic Meningitis Syndrome
Abdominal pain	2	Unlabeled
Pain in extremity	2	Unlabeled

Xembify, USPI, updated December 29, 2020

Overall, there were very few non-fatal serious reports. The unlabeled PTs for *abdominal pain* and *pain in extremity* are non-specific and may occur with many conditions, including the labeled events of thrombosis or local adverse reactions (infusion site erythema, infusion site pain, infusion site swelling, infusion site bruising, infusion site nodule, infusion site pruritus, infusion site induration, infusion site scab, infusion site edema). No new safety concerns were identified.

6.2.3 Non-serious Reports

During the reporting period, there were 39 non-serious reports; of which 3 reports involved pediatric patients. The most frequently reported PTs occurring in > 2 non-serious reports are shown in Table 4 and are labeled events. Note that a report may have one or more PTs.

Table 4: Top PTs for non-serious reports

Preferred Term (PT)	Number of reports	Label status
Headache	5	*Severe headache* is labeled under Warnings and Precautions, section 5.3 Aseptic Meningitis Syndrome
Nausea	4	Labeled under Warnings and Precautions, section 5.3 Aseptic Meningitis Syndrome

Xembify, USPI, updated December 29, 2020

PTs occurring in pediatric reports include pyrexia (*fever* is labeled under Warnings section 5.3 Aseptic Meningitis Syndrome); injection site discomfort (labeled as *infusion site discomfort* in 6.1 Clinical Trials Experience), and muscle spasms (unlabeled non-specific event).

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Xembify 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 for the data mining analysis as of October 29, 2021. 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. 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 three PTs, summarized in the table below, with a disproportional reporting alert. Note that a report may have one or more PTs.

Preferred Term (PT)	Label status
Headache	*Severe headache* is labeled under Warnings and Precautions, section 5.3 Aseptic Meningitis Syndrome
Infusion site erythema	Labeled (6.1 Clinical Trials Experience)
Infusion site pain	Labeled (6.1 Clinical Trials Experience)

Xembify, USPI, updated December 29, 2020

All three PTs are labeled events for Xembify. There are no new safety concerns from review of data mining results.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Xembify covering the surveillance period were reviewed. The adverse events reported were consistent with those seen in the 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 U.S. National Library of Medicine's PubMed.gov database on November 16, 2021, for peer-reviewed literature, with the search term "Xembify" and published dates between July 3, 2019 and November 15, 2021, retrieved 3 articles. Titles and abstracts were reviewed for relevance to safety information for Xembify, and one article relevant to safety was identified and is summarized below. No new safety concerns were identified.

Table 5: Summary of safety conclusion in published literature

Article	Authors' safety conclusion
Sleasman JW, Lumry WR, Hussain I, Wedner HJ, Harris JB, Courtney KL, Mondou E, Lin J, Stein MR. Immune globulin subcutaneous, human - klhw 20% for primary humoral immunodeficiency: an open-label, Phase III study. Immunotherapy. 2019 Nov;11(16):1371-1386. doi: 10.2217/imt-2019-0159. Epub 2019 Oct 17. PMID: 31621458.	Presents data from the prospective, phase 3 study of Xembify in patients with primary humoral immunodeficiency. About 33 subjects reported 79 adverse events during run-in and IV phases; 41 subjects reported 141 adverse events during the SC phase, with most being local infusion site reactions. The majority of infusion site reactions were mild to moderate in severity. The authors conclude that IGSC-C 20% (Xembify) was bioequivalent to IGIV-C 10% and was well tolerated, with a safety profile comparable with IGIV-C 10%.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Xembify does not indicate any new safety concerns. The PAC review was initiated due to the July 3, 2019 approval of Xembify for the treatment of primary humoral immunodeficiency in patients 2 years of age and older. In general, there were very few pediatric reports (all non-serious events) during this review period. 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 Xembify.