Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)

PHARMACOVIGILANCE SUPPLEMENTAL BLA MEMORANDUM

From:	Deborah Thompson, MD, MSPH Medical Officer, Team Lead Pharmacovigilance Branch 3 (PB3) DPV, OBPV, CBER, FDA
To:	Hongloan La, MD Chair Review Committee Office of Therapeutic Products (OTP)
Through:	Kerry Welsh, MD, PhD Branch Chief, PB3 Meghna Alimchandani, MD Deputy Division Director, DPV OBPV, CBER, FDA
Subject:	Review of Supplemental BLA Pharmacovigilance Plan and Postmarketing Experience Labeling Changes
Sponsor:	Grifols Therapeutics, LLC
Product:	Xembify (immune globulin subcutaneous, human - klhw) 20% solution
Application Type/Number:	sBLA 125683/265
Approved Indication:	Treatment of Primary Humoral Immunodeficiency in patients 2 years of age and older
Submission Date:	September 18, 2023
Action Due Date:	July 18, 2024

1 Objective

The purpose of this review is to assess the adequacy of the sponsor's revised Risk Management Plan (RMP) and proposed changes to the U.S. Package Insert (USPI) Section 6.2 Postmarketing Experience which were submitted under efficacy supplement sBLA 125683/265. OBPV defers to OTP for review of the USPI proposed label changes beyond Section 6.2. Our review will determine whether any safety-related studies, such as Postmarketing Requirements (PMRs) and/or Postmarketing Commitments (PMCs), or REMS are warranted, should this sBLA be approved. Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

2 Product Information

2.1 Product Description and Approved Indication

Per the USPI, Xembify is a 20% "ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for subcutaneous (SC) administration. The purity is ≥98% IgG with a sub-class distribution similar to that found in normal serum." The product contains "18% to 22% protein in 0.16 to 0.26 M glycine and 10 to 40 mcg/ml polysorbate 80 at a pH of 4.1 to 4.8." Xembify is manufactured "from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography." The product contains no preservatives and is not made using natural rubber latex.

2.2 Approved Indication

Xembify is approved in the U.S. for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Reviewer comment: The sponsor does not propose changes to the indication for use of Xembify in this sBLA. Changes are proposed for the dosage and administration of Xembify, including biweekly dosing for patients switching from either an intravenous immune globulin or subcutaneous immune globulin, addition of loading and maintenance dosing for treatment-naïve patients, and an increase to the maximal subcutaneous infusion rate.

3 Pertinent Regulatory History

Xembify (BLA 125683/0) was approved in the U.S. on July 3, 2019 for the indication of PI. Xembify is approved in 12 countries worldwide, including Australia, Canada, Czech Republic, Finland, France, Germany, Italy, Slovakia, Spain, Sweden, United Kingdom, and U.S. As of September 30, 2023, Xembify has been distributed in the U.S. and Spain.

4 DESCRIPTION OF XEMBIFY CLINICAL TRIAL SAFETY DATABASE

The sponsor submitted clinical safety data for treatment of individuals with PI using Xembify from two Phase 3 studies (GTI1502 in North America and GIT1503 in the European Union and Australia) and one Phase 4 study (GC1906 in the U.S.) (Table 1). OBPV defers to the product office on final review of the clinical database for this sBLA, including safety and efficacy outcomes, which will inform the final language in the USPI. A *focused* review of the sponsor's data initially submitted to the sBLA was performed to inform decisions pertaining to pharmacovigilance activities, should this sBLA 125683/265 be approved.

Table 1: Summary of Clinical Studies for Xembify*

Study ID	**Study Design**	**Dose Adjustment Factor**	**Study and Control Treatments, Dose**	**No. of Subjects in Safety Population**
GTI1502	Prospective, multi-center, open-label, single-sequence, 6-month, PK, safety, and tolerability	IV infusion of IGIV-C 10%**:** SC infusion of IGSC 20% (1:1.37)	Run-in IGIV-C 10% phase if needed for steady state with 2 IV infusions of IGIV-C 10% in the IV PK phase followed by 24 weekly SC infusions of IGSC 20% in the SC phase	53 (52 subjects in IV phase, 49 subjects in SC phase)
GTI1503	Prospective, multi-center, open-label, single-arm, efficacy, PK, safety, and tolerability study	Previous regimens**:** IGSC 20% (1:1)	IGSC 20%, minimum dose: 100 mg/kg/week; a total of 52 weekly SC doses in the SC phase	61 in SC phase
GC1906	Multi-center, single-sequence, open-label, 2 cohorts, efficacy, PK, safety, and tolerability study	Treatment-Experienced Subjects Cohort SC infusion of IGSC 20% If entering on SC commercial immune globulin 1:1 If entering on IV commercial immune globulin) 1:1.37	Treatment-Experienced Subjects Cohort Treatment Period 1: 16 weekly doses of IGSC 20% from Week 0 to Week 15; Treatment Period 2: 9 biweekly (every 2 weeks) doses of IGSC 20% from Week 16 to Week 32.	33 (27 treatment-experienced subjects; 6 treatment-naïve subjects)

			Treatment-naïve Subjects Cohort A loading dose of IGSC 20% (150 mg/kg/day) from Days 1 to 5 (Week 0) followed by weekly maintenance infusions of IGSC 20% 150 mg/kg starting Week 1 (Day 8) through Week 32	

*Adapted from Table 1-1, Summary of Clinical Safety, STN 125683/265, Module 2.7.4

Study GTI1502

The majority (n=41, 83.7%) of participants in the SC phase experienced adverse events (AEs); two (4.1%) participants experienced serious AEs (SAEs). The most common AEs were sinusitis (n=9, 18.4%), infusion site nodule (n=6, 12.2%), upper respiratory tract infection (n=5, 10.2%), and 3 (6.1%) events each of bronchitis, cough, diarrhea, infusion site bruising, infusion site pain, and streptococcal pharyngitis. Two participants in the SC phase experienced the following SAEs: one participant experienced animal bite, cellulitis, and sepsis and one participant experienced intervertebral disc degeneration. All SAEs were assessed as unrelated to the product by the study investigators. There were no deaths reported.

Study GTI1503

The majority (n=52, 85.2%) of participants in the SC phase experienced AEs; 7 (11.5%) participants experienced SAEs. The most common AEs were nasopharyngitis (n=12, 19.7%), infusion site erythema (n=10, 16.4%), 9 (14.8%) events each of cough and upper respiratory tract infection, 8 (13.1%) events each of bronchitis and infusion site pruritis, 7 (11.5%) events each of headache, pyrexia, rhinitis, and sinusitis, 6 (9.8%) events each of diarrhea and gastroenteritis, and 5 (8.2%) events each of arthralgia, infusion site pain, lower respiratory tract infection, and vomiting.

Seven participants in the SC phase experienced the following SAEs: urinary tract infection, nephrotic syndrome, medical device site joint infection, joint dislocation, thrombocytopenia, aortic valve incompetence, and pneumonia. All SAEs were assessed as unrelated to the product by the study investigators. There were no deaths reported.

Study GC1906

The most common AEs (≥5%) in Study GC1906 are shown by treatment experience and dosing schedule in Table 2.

Table 2: Incidence of Treatment-Emergent Adverse Events by Preferred Term in ≥5% of Participants in Study GC1906†

Preferred Term	Treatment-Experienced: Weekly Dosing (N=27)	Treatment-Experienced: Biweekly Dosing (N=25)	Treatment-Naive (N=6)
Total Number of Subjects with at Least 1 TEAE, n (%)	16 (59.3)	12 (48.0)	3 (50.0)
Headache, n (%)	3 (11.1)	0	1 (16.7)
Procedural Pain, n (%)	1 (3.7)	1 (4.0)	1 (16.7)
Infusion Site Pain, n (%)	1 (3.7)	1 (4.0)	0
Infusion Site Reaction, n (%)	0	0	1 (16.7)
Infusion Site Scab, n (%)	0	0	1 (16.7)
Asthma, n (%)	1 (3.7)	1 (4.0)	0
Dehydration, n (%)	1 (3.7)	1 (4.0)	0
Back Pain	0	1 (4.0)	1 (16.7)
Compression Fracture, n (%)	0	0	1 (16.7)
Contusion, n (%)	0	0	1 (16.7)
Upper Limb Fracture, n (%)	0	0	1 (16.7)
Plantar Fasciitis, n (%)	0	0	1 (16.7)
Vitamin B12 Deficiency, n (%)	0	0	1 (16.7)
Skin Mass, n (%)	0	0	1 (16.7)
Bartholin's Cyst, n (%)	0	0	1 (16.7)

†Excerpted from Table 4-2, Summary of Clinical Safety, STN 125683/265, Module 2.7.4

Among treatment-experienced participants, there were four participants who experienced SAEs: one participant each who experienced dehydration, acute pancreatitis, and worsening of Barret's esophagitis and one participant who experienced two SAEs that led to hospitalizations for three infections (viral pneumonia during weekly dosing period and *Clostridium difficile* and cellulitis during biweekly dosing period). There was also one treatment-naïve participant who experienced a compression fracture with back pain. All non-infectious SAEs were considered by investigators as unrelated to treatment. The SAEs of *Clostridium difficile* and cellulitis were considered possibly related to treatment by investigators. There were no deaths reported in Study GC1906.

Reviewer comment: Overall, across the three clinical studies, the most common AEs were consistent with events that occur with SC infusions or the underlying condition of PI. SAEs occurred infrequently and were mostly considered by study investigators as unrelated to treatment with the product. The studies also assessed for "other significant adverse events" which included serious bacterial infections, infections of any kind, validated infections, days on antibiotics, hospitalizations, days of work/school/daily activities missed due to infections and related treatment, and treatment emergent AEs that led to withdrawal of participants from the study. No new safety concerns were identified in clinical studies for Xembify that need to be addressed from the pharmacovigilance perspective. Please see the clinical review memo for a summary of

FDA's review of safety data for Xembify. Please refer to the package insert for the final clinical safety data.

5 SUMMARY OF SPONSOR'S PROPOSED LABEL CHANGES TO SECTION 6.2 POSTMARKETING EXPERIENCE

The sponsor proposed changes to Section 6.2 Postmarketing Experience are shown below (proposed additions are underlined):

The following adverse reactions have been identified and reported during the postmarketing use of immune globulin products administered subcutaneously:

Immune system disorders: Anaphylactic reaction, hypersensitivity

Nervous system disorders: Tremor, dizziness and paresthesia

Cardiac disorders: Tachycardia

Vascular disorders: Hypotension

Respiratory, thoracic and mediastinal disorders: Dyspnea and laryngospasm

General disorders and administration site conditions: Chills, fatigue and pain

Reviewer comment: The Xembify USPI Section 6.2 Postmarketing Experience currently includes adverse reactions reported during postmarketing use of immune globulin products administered subcutaneously (i.e., class effects). Please see the final package insert submitted by the sponsor for final agreed upon language.

6 SUMMARY OF U.S. AND FOREIGN POSTMARKETING EXPERIENCE

6.1 Sponsor's Analysis

The sponsor's Summary of Clinical Safety (SCS) indicated that as of May 11, 2023, 82 spontaneous postmarketing cases had been received. The most frequently occurring AEs at the MedDRA Preferred Term (PT) level included dizziness, anaphylactic reaction/hypersensitivity, chills, hypotension, pain, and fatigue; the sponsor proposes adding these most frequently occurring PTs to the USPI Section 6.2 Postmarketing Experience.

Reviewer comment: The sponsor did not provide additional information regarding postmarketing data nor further rationale for their proposal to add PTs to the USPI Section 6.2 Postmarketing Experience. An IR was sent asking for additional details regarding the postmarketing data, including number of U.S. and foreign reports, serious reports, counts of PTs, time to event onset, narratives for death reports, information on

the co-occurrence of AEs, and a causality assessment and rationale for the updates to the USPI Section 6.2. The sponsor was also asked to clarify where the product has been distributed. The sponsor's IR response (STN 125683/265.2) is summarized below.

Summary of Sponsor's Postmarketing Data from Response to DPV IR #1

The sponsor's IR response (STN 125683/265.2, sequence 0234) indicated that a total of 83 spontaneous postmarketing cases had been received for Xembify as of May 11, 2023 (one case was received May 10, 2023 and was entered into the safety database after the first data extraction was performed). All reports were from the U.S. and eight reports were serious (no fatal reports). Report counts for the most frequently reported PTs were as follows: headache (n=14), diarrhea (n=9), nausea (n=9), infusion site erythema (n=8), infusion site swelling (n=8), fatigue (n=7), injection site pain (n=6), erythema (n=5), infusion site pain (n=5), and pruritis (n=5). Among serious reports, the sponsor reported that the most frequently reported PTs were headache and aseptic meningitis (2 reports for each). The 83 reports included a total of 240 events with almost half (n=119, 49.6%) of the events occurring ≤30 days from product administration.

The sponsor provided brief summaries of postmarketing data for the seven AEs proposed for inclusion in the USPI Section 6.2:

- Anaphylactic reaction and hypersensitivity:
  - 1 case of anaphylactic reaction associated with symptoms of pruritis, swelling, and paresthesia (serious report)
  - 15 reports identified under Hypersensitivity SMQ, including symptoms of urticaria, pruritis, rash, swelling tongue, flushing, erythema, skin reaction, sneezing, and periorbital swelling
- Dizziness:
  - 4 cases that also include other reported events, including 3 cases with hypersensitivity events (i.e., swollen tongue, rash, urticaria) and 1 case with diarrhea, nausea, headache, anxiety, and fatigue
- Chills, fatigue, and pain:
  - No cases reported for chills – sponsor reports chills is included in the "EU core of Summary of Product Characteristics" as a class effect
  - 7 cases of fatigue in combination with other events such as dizziness, swollen tongue, headache, migraine, myalgia, fibromyalgia, muscle spasm, asthenia, diarrhea, nausea, anxiety, malaise, erythema, pain, and infusion site reactions
  - 4 cases of pain alone
  - Other types of pain events include injection site pain (5), infusion site pain (4), abdominal pain (3), oropharyngeal pain (2), back pain (1), neck pain (1), pain in extremity (1), spinal pain (1), and chest pain (1)
- Hypotension:
  - 1 case of hypotension reported with other events of rash, headache, nausea, dizziness, heart rate increased, and urticaria

The sponsor commented that the seven new AEs are "included as they are class effect and all but one (chills) were reported in the postmarketing setting as related to the administration of the product." In addition, four of the events (fatigue, anaphylaxis, hypersensitivity, and low blood pressure) are already included in the USPI Section 17 Patient Counseling Information. The sponsor indicated that class effect events are "considered necessary to give complete information to healthcare professionals."

Reviewer comment: There is precedent for adding class effect AEs to the USPI Section 6.2 Postmarketing Experience for other SC immune globulin products, including AE statements focused on SC immune globulin products and AEs following use of immune globulin products more broadly. The seven PTs proposed by the sponsor for addition to the Xembify USPI Section 6.2 appear in other SC immune globulin product labels (Section 6.2) either as class effect AEs and/or AEs occurring after use of the specific product.

6.2 Analysis of FDA Postmarketing Safety Data

6.2.1 FAERS Reports

A cumulative FAERS query was conducted on November 16, 2023 for AE reports following administration of Xembify (Product Name). The FAERS query returned 99 cases (all U.S.), including 24 serious reports; there were no fatal cases. Among cases with an age reported (n=57), 35 cases were aged 17-65 years, 15 cases were aged ≥65 years, and 7 cases were aged <17 years.

Among the 99 total reports, the most frequently reported PTs (≥5 reports) were headache (17), nausea (12), diarrhoea (8), infusion site erythema (8), pain (8), infusion site swelling (7), pruritis (7), swelling (7), injection site pain (6), malaise (6), erythema (5), fatigue (5), infusion site pain (5), infusion site pruritis (5), infusion site reaction (5), and pyrexia (5). Among the 24 serious reports, the most frequently reported PTs (>1 report) included headache (6), malaise (3), nausea (3), pain (3), pain in extremity (3), product dose omission issue (3), abdominal pain (2), COVID-19 (2), chills (2), diarrhoea (2), hypoaesthesia (2), injection site pain (2), insurance issue (2), meningitis aseptic (2), pneumonia (2), pruritis (2), pulmonary embolism (2), swelling (2), tinnitus (2), and urinary tract infection (2).

In addition, among PTs proposed by the sponsor for inclusion in Section 6.2 that are not listed in the paragraph above, the FAERS query returned three reports with the PT dizziness (all non-serious), one report with the PT anaphylactic reaction (serious), and one report with the PT hypotension (non-serious and also included the PTs rash, headache, nausea, dizziness, heart rate increased [tachycardia], and urticaria). A separate cumulative FAERS query conducted on November 28, 2023 using the Hypersensitivity SMQ (Narrow) returned 17 reports, including two expedited 15-day reports. Furthermore, a separate cumulative FAERS query conducted on May 22, 2024 revealed that the following PTs not listed elsewhere in this memo have been reported following administration of Xembify, in addition to being labeled as class effects for

subcutaneous immunoglobulin products: dyspnea (6), chest discomfort (3), and paraesthesia (2).

FAERS query results for the seven AEs that the sponsor proposes adding to Section 6.2 are summarized as follows:

- Anaphylactic reaction and hypersensitivity:
    - 1 case of anaphylactic reaction associated with symptoms of pruritis, swelling, and paresthesia (serious report)
    - 17 reports returned under Hypersensitivity SMQ (2 of which were expedited 15-day reports), including symptoms of urticaria, itching, rash, swollen tongue, swelling face, eye swelling, periorbital swelling, flushing, erythema, skin reaction, and hypotension
- Dizziness:
    - 3 cases (all non-serious) that also include other reported events, including 2 cases with hypersensitivity events (i.e., swelling, rash, flushing, pruritis, urticaria, and/or hypotension) and 1 case with diarrhea, nausea, anxiety, and fatigue
    - 1 additional report (periodic report) with the PT dizziness was returned in the Hypersensitivity SMQ (Narrow) query (conducted on November 28, 2023) which included AEs of swollen tongue, headache, fatigue, myalgia, and muscle spasms
- Chills, fatigue, and pain:
    - 2 cases of chills (both serious) that include other PTs such as pain, swelling, pyrexia, nausea, headache, fatigue, diarrhea, and/or colitis ulcerative
    - 5 cases of fatigue (1 serious) in combination with other events such as dizziness, headache, asthenia, diarrhea, nausea, anxiety, malaise, infusion site erythema/swelling/pruritis, and/or infusion site reactions.
    - 8 cases with the PT pain (3 serious)
    - Other types of pain events including injection site pain (6), infusion site pain (5), abdominal pain (4), back pain (1), neck pain (1), pain in extremity (3), spinal pain (1), chest pain (1), and bone pain (1)
- Hypotension:
    - 1 case of hypotension reported (non-serious) as “measured blood pressure which was low” along with other reported events (including possible hypersensitivity events) of rash, headache, nausea, dizziness, heart rate increased, and urticaria; individual was seen in the emergency room for low blood pressure and heart rate increased [tachycardia] and was treated with steroids, Benadryl, pain reliever for headache, and intravenous fluids

<u>Reviewer comment:</u> There are FAERS reports for each of the seven AEs (anaphylactic reaction, hypersensitivity, dizziness, chills, fatigue, pain, and hypotension) that the sponsor proposes to add to the Xembify USPI Section 6.2 Postmarketing Experience. Overall, there are a limited number of reports for each PT and some PTs only have non-

serious reports. Most PTs are reported in combination with other PTs, including three reports of dizziness and the one report of hypotension which include PTs consistent with possible hypersensitivity reactions. Section 17 Patient Counseling Information lists low blood pressure as a sign of a hypersensitivity reaction.

Among the most frequently reported serious events in FAERS, Xembify is labeled for infusion site pain which is related to injection site pain and could be related to pain in extremity or possibly to abdominal pain (product can be administered in the abdomen, thigh, upper arm, sides, back and/or lateral hip). Xembify is also labeled for diarrhea, pneumonia (i.e., serious bacterial infections including bacterial pneumonia), and infusion site swelling.

There is a Boxed Warning indicating that "thrombosis may occur with immune globulin products, including XEMBIFY"; pulmonary embolism is not specifically labeled. Section 17 Patient Counseling Information lists symptoms of thrombosis including symptoms that could be consistent with a pulmonary embolism such as unexplained shortness of breath and chest pain or discomfort that worsens on deep breathing. The two serious reports of pulmonary embolism following Xembify contain limited clinical details which preclude further assessment. This reviewer notes that the USPI for Cutaquig includes "thromboembolism" and "pulmonary embolism" in Section 6.2 as AEs reported during postmarketing use of immune globulin products, although not specifically for subcutaneous immune globulin products.

Xembify is also not specifically labeled for headache or nausea other than as possible symptoms of aseptic meningitis syndrome (Warnings and Precautions, Section 5.3 Aseptic Meningitis Syndrome). However, the sponsor's draft label proposes to add headache and nausea to Section 6.1. For aseptic meningitis, the FAERS search returned two serious postmarketing reports, and DPV recommends the addition of aseptic meningitis to the USPI Section 6.2 Postmarketing Experience. Please see Section 7 of this memo for additional information on IR correspondence with the sponsor regarding aseptic meningitis.

In addition, urinary tract infection is not specifically labeled although serious bacterial infections are labeled; urinary tract infections could also be confounded by indication. COVID-19 is also an infection that is confounded by indication. Product dose omission and insurance issue are product use/access issues, rather than product-related safety concerns.

Chills (sponsor proposes to add to Section 6.2), malaise (non-specific event possibly related to fatigue which sponsor proposes to add to Section 6.2), pruritis (related to hypersensitivity which sponsor proposes to add to Section 6.2), hypoaesthesia, and tinnitus are currently unlabeled events. Among the total of three reports of hypoaesthesia, concomitant AEs included one case with pseudostroke and nausea, one case with painful numbness in the arm while sleeping and chest pain, and one case with a possible hypersensitivity reaction with symptoms including dizziness, rash, nausea, swelling, erythema, flushing, and pruritis. The two reports of tinnitus included one case

with concomitant conditions including pancreatic carcinoma, COVID-19, ear infection, sinusitis, and ear pain and echoing and one case with pain, swelling, pyrexia, chills, nausea, headache, and off label use of the product for iron deficiency anemia, Sicca syndrome, and cerebellar ataxia. Hypoaesthesia and tinnitus are not listed as class effect AEs in other subcutaneous immune globulin products (i.e., Hizentra, Cutaquig, Cuvitru, and Hyqvia) and the sponsor does not propose adding hypoaesthesia or tinnitus to the Xembify USPI. Please see the package insert submitted by the sponsor for the final agreed upon language for the USPI.

FAERS reports may include one or more PTs. FAERS queries were run via automated queries and for the purposes of this memo not all cases were individually reviewed to clinically confirm event occurrence or assess causality. In addition, spontaneous surveillance systems such as FAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding dosing, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was due to the product.

6.2.2 Data mining

Data mining for Xembify was conducted using the Empirica Signal FAERS Product Name (S) PT run on November 29, 2023. The data lock point was November 26, 2023. Data mining identified the following PTs with disproportional reporting values (EB05 ≥2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean): headache, infusion site bruising, infusion site erythema, infusion site nodule, infusion site pain, infusion site pruritis, infusion site reaction, infusion site swelling, injection site swelling, and swelling.

<u>Reviewer comment:</u> The sponsor proposes to add headache to the Xembify USPI Section 6.1. DPV defers to OTP for labeling changes proposed for Section 6.1. Infusion site bruising, infusion site erythema, infusion site nodule, infusion site pain, infusion site pruritis, and infusion site swelling are currently labeled events in Section 6.1. Injection site swelling and swelling are PTs related to infusion site swelling. Infusion site reactions are local reactions related to currently labeled events (as described above) and also include warmth and induration at the injection/infusion site. No new safety concerns were identified through data mining that suggest the need for additional pharmacovigilance activities for Xembify.

Data mining is subject to limitations including the limits of spontaneous surveillance systems described in the section above. There may be confounding by indication or false alerts from concomitant product administration. In addition, a signal may be reflected in multiple PTs that individually do not reach alert threshold.

7 SPONSOR'S PHARMACOVIGILANCE PLAN

The sponsor submitted an EU Risk Management Plan (RMP) (version 3.0, dated February 8, 2023, version 3.0-USA-1, dated December 5, 2023, and version 3.0-USA-2, dated December 28, 2023) which proposes routine pharmacovigilance (PV), including a follow-up questionnaire for serious injection site reactions, and routine risk minimization activities (i.e., labeling) (Table 3).

Table 3. Summary of Sponsor's Risk Management Plan*

Type of Concern	Safety Concern	Proposed Action
Important identified risk	Infusion site reactions	Routine PV and risk minimization activities Follow-up questionnaire for serious injection site reactions
Important identified risk	Hypersensitivity reactions including anaphylactic reactions	Routine PV and risk minimization activities
Important identified risk	Aseptic meningitis	Routine PV and risk minimization activities
Important potential risk	Thromboembolic events	Routine PV and risk minimization activities
Important potential risk	Theoretical risk of pathogen infection	Routine PV and risk minimization activities
Important potential risk	Interaction with live attenuated vaccines	Routine PV and risk minimization activities
Important potential risk	Medication errors arising from self-administration	Routine PV and risk minimization activities
Missing information	Use in women who are pregnant or lactating	Routine PV and risk minimization activities

*Adapted from Table Part V.3, Risk Management Plan (version 3.0-USA-1, dated December 5, 2023), STN 125683/265.4, Module 1.16.

<u>Reviewer comment:</u> The sponsor does not propose any postmarketing safety studies or REMS for Xembify. The RMP indicates that significant changes in RMP version 3.0 (dated February 8, 2023) includes postmarketing safety data updated to December 17, 2022 with "no impact on safety concerns removal or change." The RMP also includes the added activity of having a follow-up questionnaire for serious injection site reactions.

The following IR (DPV IR #2) was sent to the sponsor regarding the RMP (version 3.0, dated February 8, 2023) and postmarket data:

We are reviewing your submission for Xembify (sBLA 125683/265) and have the following questions and comments:

1. In your Information Request (IR) response regarding postmarket data for Xembify (STN 125683/265.2, sequence 0234; received on November 14, 2023), you report eight serious cases for Xembify. Please provide a summary and count of each PT reported for the eight serious cases.
2. We note that cases of hypersensitivity, including anaphylaxis, have occurred in the postmarket setting following administration of Xembify and that you propose to include anaphylactic reactions and hypersensitivity in the USPI Section 6.2 Postmarketing Experience. Please update the Risk Management Plan (RMP) to include hypersensitivity reactions, including anaphylactic reactions, as an important identified risk or provide rationale for why hypersensitivity reactions, including anaphylactic reactions, should remain an important potential risk.
3. We note your plan in the RMP to use a follow-up questionnaire for serious injection site reactions with Xembify (page 39-40). The RMP (page 40) indicates that the "evaluation of effectiveness of risk minimization activities will be seen in the frequency of reporting adverse events related to injection site reactions. A low frequency of cases will show a correct application and understanding of this additional risk minimization activities." It is unclear how asking for additional information about already reported cases will by itself minimize the risk of future cases. How will a low frequency of cases show correct application and understanding of this additional risk minimization activity versus represent under-reporting of adverse events? In addition, is the follow-up questionnaire for serious injection site reactions a risk minimization activity or a routine pharmacovigilance activity? Please clarify.
4. In addition, we note you submitted an EU RMP that specifies product indications and dosage in the EEA. Please add a section to the RMP to specify product indications and dosage in the U.S.

The sponsor's IR response to DPV IR #2 (STN 125683/265.4) provided a summary of the eight serious reports for Xembify, which included two spontaneous reports of aseptic meningitis (U.S. report for a 48-year-old female who experienced aseptic meningitis, painful injection sites, and abdominal distension with an unknown outcome [FAERS #18433254] and U.S. report for a 44-year-old female who experienced aseptic meningitis with an outcome of recovered [FAERS report #23175858]). At the time of DPV IR #2, aseptic meningitis was listed in the RMP as an important potential risk. The sponsor clarified that "Hypersensitivity reactions, including anaphylactic reactions" are an important identified risk, rather than an important potential risk. The sponsor further clarified that the follow-up questionnaire for serious injection site reactions is a routine pharmacovigilance activity rather than a risk minimization measure. In addition, the sponsor updated the RMP to include product indications and dosage in the U.S. and submitted a revised RMP (version 3.0-USA-1, dated December 5, 2023).

A follow-up IR (DPV IR #3) was sent:

In your IR response (STN 125683/265.4, sequence 0243) submitted on December 8, 2023, there were two serious postmarket reports of aseptic meningitis following administration of Xembify. The report summaries indicate that one case was "considered serious and overall expected" and the other case was "considered serious and expected." Please comment and provide rationale regarding whether aseptic meningitis should be listed in the Risk Management Plan (RMP) as an Important Identified Risk rather than an Important Potential Risk. Please respond to this IR and submit a revised RMP, if appropriate, by January 10, 2024.

The sponsor's response to DPV IR #3 (STN 125683/265.5) indicated that the sponsor updated the RMP to change aseptic meningitis from an important potential risk to an important identified risk. The sponsor's IR response is acceptable.

A follow-up IR (DPV IR #4) was sent:

We are reviewing your revised Risk Management Plan (RMP, version 3.0-USA-2) for Xembify (STN 125683/265.5) and note that there were two serious spontaneous reports of aseptic meningitis in the postmarket setting described on page 26 (track change version). Page 29 indicates there were a total of five ICSRs for aseptic meningitis reported with Xembify in the postmarket setting, including two solicited cases. Please clarify the total number of serious and non-serious reports of aseptic meningitis following administration of Xembify in the postmarket setting (spontaneous and solicited reports). Please confirm that all five cases of aseptic meningitis were reported to FAERS and provide the FAERS ID numbers.

Please respond to this Information Request by COB January 18, 2024 and provide a revised RMP, if needed (track change and clean versions).

The sponsor's IR response (STN 125683/265.7) clarified the total number of serious and non-serious reports with the PT aseptic meningitis following administration of Xembify in the postmarket setting as follows: two serious spontaneous reports (up to November 2023) and one non-serious solicited report of aseptic meningitis. The sponsor submitted a revised RMP (version 3.0-USA-3, dated January 11, 2024) which reflected the clarification of reports for aseptic meningitis.

Reviewer comment: The sponsor's revised RMP (version 3.0-USA-3, dated January 11, 2024) now includes the important identified risks of hypersensitivity reactions, including anaphylactic reactions, and aseptic meningitis which were previously listed as important potential risks. The USPI includes Warnings and Precautions for Hypersensitivity (Section 5.1) and Aseptic Meningitis Syndrome (Section 5.3); there is also information on signs and symptoms of hypersensitivity and aseptic meningitis in Section 17 Patient Counseling Information. Hypersensitivity reactions, including anaphylactic reactions, and cases of aseptic meningitis have occurred in the postmarket setting. The RMP is appropriate to monitor the risks of hypersensitivity reactions and aseptic meningitis. The sponsor's IR responses and revised RMP are acceptable.

8 DPV ASSESSMENT

The sponsor submitted an efficacy supplement for Xembify (sBLA 125683/265) which includes proposed changes for the dosage and administration of Xembify, a revised RMP, and proposed changes to the USPI Section 6.2 Postmarketing Experience. OBPV/DPV defers to OTP for review of changes to the USPI beyond Section 6.2. The RMP includes routine pharmacovigilance and risk minimization activities. The sponsor's revised RMP includes updating hypersensitivity reactions, including anaphylactic reactions, and aseptic meningitis from important potential risks to important identified risks. Cases of hypersensitivity reactions, including anaphylactic reactions, and aseptic meningitis have been reported in the postmarket setting for Xembify. Hypersensitivity and aseptic meningitis syndrome are labeled in Warnings and Precautions.

The sponsor proposes the addition of seven AEs (anaphylactic reaction, hypersensitivity, dizziness, chills, fatigue, pain, and hypotension) to the USPI Section 6.2. There are FAERS reports for each of these seven AEs and these AEs have also been known to occur following administration of other immune globulin products. Review of the data submitted by the sponsor and from FAERS support the revisions to the RMP and the addition of the proposed AEs to the USPI Section 6.2 Postmarketing Experience. Review of the data for Xembify did not reveal findings that warrant a REMS or FDAAA Title IX safety PMR or PMC study.

9 DPV RECOMMDENDATIONS

Should the sBLA be approved, the sponsor's RMP (version 3.0-USA-3, dated January 11, 2024) is adequate. There will be routine pharmacovigilance, which includes AE reporting in accordance with 21 CFR 600.80, and routine PV activities beyond AE reporting and signal detection (i.e., follow-up questionnaire for serious injection site reactions). The sponsor's proposed changes to the USPI Section 6.2 Postmarketing Experience are acceptable. Also, DPV recommends the addition of aseptic meningitis to the Section 6.2. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon content and language.

Appendix: Materials Reviewed

Table A1: Materials Reviewed in Support of Pharmacovigilance Assessment

Date	Source	Document Type	Document(s) Reviewed
July 3, 2019	FDA	STN 125683/0	Xembify BLA Approval Letter
September 18, 2023	Sponsor	STN 125683/265 (seq 0204)	Module 1.16, Risk Management Plan, version 3.0, dated February 8, 2023
September 18, 2023	Sponsor	STN 125683/265 (seq 0204)	Module 1.14 Draft Labeling Text
September 18, 2023	Sponsor	STN 125683/265 (seq 0204)	Module 2.5 Clinical Overview
September 18, 2023	Sponsor	STN 125683/265 (seq 0204)	Module 2.7.4 Summary of Clinical Safety
November 14, 2023	Sponsor	STN 125683/265.2 (seq 0234)	Module 1.12.11 IR response to DPV IR #1 regarding postmarket data
December 8, 2023	Sponsor	STN 125683/265.4 (seq 0243)	Module 1.12.11 IR response to DPV IR #2 regarding PTs for postmarket serious reports and clarifications/revisions to the RMP
December 8, 2023	Sponsor	STN 125683/265.4 (seq 0243)	Module 1.16 Updated Risk Management Plan, version 3.0-USA-1, dated December 5, 2023
January 9, 2024	Sponsor	STN 125683/265.5 (seq 0249)	Module 1.12.11 IR response to DPV IR #3 regarding clarifications/revisions to the RMP for aseptic meningitis
January 9, 2024	Sponsor	STN 125683/265.5 (seq 0249)	Module 1.16 Updated Risk Management Plan, version 30.-USA-2, dated December 28, 2023
January 17, 2023	Sponsor	STN 125683/265.7 (seq 0254)	Module 1.12.11 IR response to DPV IR #4 regarding clarifications of total number of cases of aseptic meningitis reported in postmarket setting Module 1.16 Updated Risk Management Plan, version 3.0-USA-3, dated January 11, 2024