



Memorandum

DATE: March 8, 2019

TO: Jennifer Reed, Chair, CBER/OTAT/DPPT/PDB
Candido Alicea, RPM, CBER/OTAT/RMS

FROM: Stephanie Donahoe, RPh, MPH
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THROUGH: Lisa L. Stockbridge, Ph.D.
Branch Chief
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SUBJECT: **XEMBIFY (immune globulin subcutaneous, human - klhw)**
BLA: 125683/0
Sponsor: Grifols Therapeutics LLC

Background

The sponsor submitted:

- New Approval
- Changes Being Effected (CBE) supplement
- Prior Approval Supplement (PAS)
- Major Amendment

Submission contains:

- Prescribing Information (PI)
- Patient Package Insert (PPI)
- Package and/or container labels
- Other (Instructions for Use, etc.)

Submission Date: July 9, 2018

PDUFA Action Date: July 9, 2019

APLB Comments/Recommendations

On July 9, 2018, Grifols Therapeutics LLC submitted Biologics License Application 125683 for **XEMBIFY (immune globulin subcutaneous, human - klhw)**, a 20% solution for subcutaneous use indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. The proposed labeling was revised on November 29, 2018, and January 28, 2019.

APLB has reviewed the proposed labeling (Package Insert dated January 28, 2019, and the package and container labels dated November 29, 2018) and has the following comments from a promotional and comprehension perspective.

GENERAL

- Update the proper name to include the suffix:

XEMBIFY (immune globulin subcutaneous, human – klhw)

- The proprietary name, **XEMBIFY**, should appear in upper case letters, as it does in most SPL stylesheets.
- The product proprietary and proper names, dosage form, and route of administration constitute the ‘product title’ (see *Guidance for Industry: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format*). The proprietary and proper names appear on one line (although it can continue to another line for lengthy names), and the dosage form and the route of administration usually appear on a second line in the two-column format of the **HIGHLIGHTS**. The data standard for the dosage form of this product is: injection, for subcutaneous use. However, *subcutaneous* is in the proper name. The solution strength is a modifier of the proper name, and there is precedent to its use in the product title for immune globulin solutions.

Thus, the product title for subcutaneous immune globulin products, such as XEMBIFY would be:

XEMBIFY (immune globulin subcutaneous, human - klhw), 20% solution

- Use bold headings only when required by the regulations. Underlining or italics can be used alternatively.
- When using an acronym, spell it out at the start of each labeling section. Each section must be able to stand on its own because sections can be commuted in different SPL stylesheets.
- Consistently use one term when describing the following: healthcare professional, physician, doctor, or nurse.
- Avoid vague terms such as ‘severe’ that do not have established definitions.
- To improve comprehension and readability, use active voice wherever possible.

HIGHLIGHTS

INDICATIONS AND USAGE

Revise the first sentence in the indications statement to the regulatory language for the product class:

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.

DOSAGE AND ADMINISTRATION

- Revise the route of administration statement to: **For subcutaneous use only.**
- If patients should be stabilized on intravenous immune globulin (IVIG) before initiating XEMBIFY (as with other subcutaneous immune globulins for PI), then the patient cannot be “naïve to immune globulin treatment.” Revise DOSAGE AND ADMINISTRATION to emphasize this. Consider placing the statement, “Before switching to XEMBIFY, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments,” at the beginning of subsection(s) Dose and/or Administration.
- The Dose subsection is cumbersome. The long paragraphs with passive voice reduce readability. Consider using a table.

WARNINGS AND PRECAUTIONS

- WARNINGS AND PRECAUTIONS in the HIGHLIGHTS should summarize information in the FULL PRESCRIBING INFORMATION. These summaries should be shortened, if necessary, to keep the HIGHLIGHTS to its half page limit (excluding BOXED WARNING).
- Verify that the WARNINGS AND PRECAUTIONS are listed in a manner consistent with the product class, and in the order of severity and public health significance. For example:
 - Hypersensitivity and anaphylactic reactions may occur. IgA deficient patients with antibodies against IgA are at greater risk of developing severe reactions.
 - Thrombosis may occur. Administer XEMBIFY at minimum dose and infusion rate practicable.
 - Monitor for renal function in patients at risk for renal failure.
 - Aseptic Meningitis Syndrome (AMS) may occur within two days of treatment.
 - Hemolysis can develop. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia.
 - Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
 - XEMBIFY is made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
 - Passive transfer of antibodies may confound serologic testing.

ADVERSE REACTIONS

The adverse reactions statement in the HIGHLIGHTS should be a simple statement of the most common adverse reactions with the cut-off frequency used. There is a regulatory definition for adverse reactions that must be used. Therefore, a definition of adverse reactions used for this label is unnecessary, possibly misleading, and reduces the readability of the information that must be conveyed in this subsection.

USE IN SPECIFIC POPULATIONS

Consider adding this section which is found in other labels in this class:

Geriatric: In patients over 65 years, do not exceed the recommended dose and infuse XEMBIFY at the minimum rate practicable. (8.5)

FULL PRESCRIBING INFORMATION: CONTENTS

Ensure that the **FULL PRESCRIBING INFORMATION: CONTENTS** aligns with the sections and subsections of the **FULL PRESCRIBING INFORMATION**.

FULL PRESCRIBING INFORMATION (FPI)

2 DOSAGE AND ADMINISTRATION

- Revise the route of administration statement to: **For subcutaneous use only.**
- Emphasize that patients must be stabilized on IVIG before switching to XEMBIFY (see above comment).
- This section has reduced readability and comprehension because of wordy paragraphs mixed with practice of medicine, overuse of passive voice, overuse of bullets, unnecessary detail, and disorganization. Consider using a table to convey the doses, dose adjustment, and administration.
- For consistency with most products in this class and similarly, as well as ease in SPL style sheet interoperability, consider using the following subsections and subsection headings for this section:

2.1 Dose

2.2 Preparation and Handling

2.3 Administration

- In the current subsection 2.1, the third bullet stating, “Do not freeze. Do not use solutions that have been frozen,” belongs in **16 HOW SUPPLIED/STORAGE AND HANDLING**.
- Do not bold sub-subsections or non-regulatory statements.
- Consider a table to illustrate, “Infusion Volume and Infusion Rate.” The parameters shown below are described in the text with one exception. The volume to be infused per site was omitted from the instructions and should be included.

| Volume to be infused SC | Rate | Number of Sites (most frequent is 4) | Site Distance Apart |
|-------------------------|--------------------------|--------------------------------------|---------------------|
| <i>Not stated</i> | ≤ 25 ml/hr/infusion site | (b) (4) | ≥ 2 inches (5 cm) |

5 WARNINGS AND PRECAUTIONS

- Warnings and precautions in this section must be listed in decreasing order of severity and public health significance. Revise this section to the class warnings and precautions.
- Subsection **5.7 Transmissible Infection Agents** has regulatory wording. (*See Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products*). Revise this subsection to the following:

Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

All infections thought to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

6 ADVERSE REACTIONS

- Place the most common adverse reactions, with a cutoff frequency, directly beneath this heading. This should include the same common adverse reactions that appear in the HIGHLIGHTS.
- Delete the definition of adverse reaction that appears in the first sentence of this section (and repeats in 6.1 Clinical Trials Experience). As defined by the regulations, “an adverse reaction is an undesirable effect reasonably associated with the use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during the use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.” (See 21 CFR 201.57(c)(7).)
- Only adverse reactions belong in this section (i.e., consider revising the last paragraph in 6.1).
- Avoid vague terms such as “mild,” “moderate,” or “severe,” that do not have established definitions.
- Include the outcome of the severe adverse reaction having non-serious polymyalgia rheumatica, as was done for intervertebral disc degeneration (*requiring orthopedic surgery*). This can be briefly described in the text.
- In Table 2, round percentages for number of subject to the nearest whole number. Use of a decimal implies that there is statistical power in the safety data to support percentages expressed as decimals.

- Include the following required language under **6.2 Postmarketing Experience**:

The following adverse reactions have been identified during post approval use of immune globulins. 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.

- **6.2 Postmarketing Experience** focuses on domestic and foreign spontaneous reports that are not addressed anywhere else in the risk information of the FPI. Therefore, anaphylactic reaction and injection site reaction should be deleted from this section.

8 USE IN SPECIFIC POPULATIONS

Revise this section to be consistent with the *Guidance for Industry: Pregnancy, Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

8.1 Pregnancy

The statement, “XEMBIFY should be given to a pregnant woman only if clearly needed,” is not informative, and should be deleted.

8.4 Pediatric Use

Avoid the term “pivotal.” This term is not easily defined, or vague. Instead, describe as a major effectiveness study.

8.5 Geriatric Use

Revise this subsection to the required regulatory language for instances where there are little or no data on geriatric patients:

Clinical studies of XEMBIFY 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

This section is lengthy and cumbersome. Frequent repetition of the proprietary name reduces readability. Consider revising the manufacturing information to be consistent with other product class prescribing information.

13 NONCLINICAL TOXICOLOGY

Organize the information under this section into the following subsections:

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

14 CLINICAL STUDIES

- Revise this section using active voice.
- Further describe the study population in terms of ethnicity (See 21 CFR 201.57 (c)(15)).

16 HOW SUPPLIED/STORAGE AND HANDLING

Consider starting this section with the following table to include NDC numbers for the package *and* container:

XEMBIFY is supplied in 1, 2, 4, and 10 gram *single use vials*.

| Package NDC Number | Container NDC Number | Size | Grams Protein |
|--------------------|----------------------|-------|---------------|
| 13533-810-05 | 13533-810-06 | 5 ml | 1 |
| 13533-810-10 | 13533-810-11 | 10 ml | 2 |
| 13533-810-20 | 13533-810-21 | 20 ml | 4 |
| 13533-810-50 | 13533-810-51 | 50 ml | 10 |

- *Components used in the packaging* are not made with natural rubber latex.
- *Continue with bullets....*

PATIENT PACKAGE INSERT (PPI)

- The dense paragraph form, high level vocabulary, passive voice, and indirect sentence structures of this PPI will reduce readability. Revise the PPI to “patient-friendly” language.
- Select one term for healthcare provider and stay consistent with the term throughout the PPI.
- Expand the population for, “Who should NOT take XEMBIFY?” Include people with history of heart or blood vessel disease, blood clots, “thick blood,” or people who have been immobile for some time.
- Under Step 13, expand the following phrase to, “Record each infusion in your journal.”

CONTAINER AND PACKAGE LABELS

Update the proper name on the labels to the include the suffix.

If you have any questions regarding this review, please contact Stephanie Donahoe, Consumer Safety Officer, at 240-402-9557.