



Memorandum

DATE: October 24, 2022

TO: Shalani Seetharaman, MS, RPM, CBER/OTAT/DRPM
Anurag Sharma, Ph.D., Committee Chair, CBER/OTAT/DCGT
Megha Kaushal, M.D., Clinical Reviewer, CBER/OTAT/DCEPT
Bettina McGraw, M.D., Clinical Reviewer, CBER/OTAT/DCEPT

FROM: Benjamin S. Cyge, Ph.D.
Consumer Safety Officer
APLB/DCM/OCBQ

THROUGH: Lisa L. Stockbridge, Ph.D.
Branch Chief
APLB/DCM/OCBQ

SUBJECT: HEMGENIX (etranacogene dezaparvovec - xxxx)
BLA: 125772/0
Sponsor: CSL Behring, LLC

Background

The sponsor submitted:

☒ New Approval
☐ Changes Being Effectuated (CBE) supplement
☐ Prior Approval Supplement (PAS)
☐ Major Amendment

Submission contains:

☒ Prescribing Information (PI)
☐ Patient Package Insert (PPI)
☒ Package and/or container labels
☐ Other

Submission Date: March 24, 2022

PDUFA Action Date: November 22, 2022

APLB Comments/Recommendations

This is a labeling review for BLA 125772, submitted by CSL Behring, LLC for HEMGENIX (etranacogene dezaparvovec - xxxx) on March 24, 2022. HEMGENIX is an adeno-associated virus vector-based gene therapy indicated to reduce the frequency of bleeding episodes (b) (4) in adults with Hemophilia B (congenital Factor IX deficiency) (b) (4) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

APLB reviewed the draft prescribing information (PI), package, and container labels dated March 24, 2022. The following comments are from a promotional and comprehension perspective.

GENERAL

- Use active voice and command language throughout the PI to increase readability.
 - Overuse of the tradename in a paragraph or section reduces readability,
 - Avoid the use of bolding unless it is required by regulation.
 - There are numerous abbreviations throughout the PI. Please ensure that each abbreviation is spelled out the first time it is used.
 - Avoid technical jargon, such as study names and numbers, Phase 1/2/3 study, primary and secondary endpoint/objective.
 - Delete the website at the end of the PI. This is a promotional link.
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HIGHLIGHTS

INDICATIONS AND USAGE

The indication, as provided in the March 24, 2022, proposed PI, is cumbersome and grammatically incorrect. For comprehension and readability, we recommend putting the information about the population together and the information regarding conditions for use together (e.g., placing all conditions for use in a parallel bulleted list). For example:

HEMGENIX is an adeno-associated virus vector-based gene therapy indicated to reduce the frequency of bleeding episodes (b) (4) in adults with Hemophilia B (congenital Factor IX deficiency) (b) (4) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

DOSAGE AND ADMINISTRATION

Consider adding the infusion rate to this section. For example,

Administer each infusion bag of HEMGENIX via intravenous infusion at a constant rate of 500 mL/hour (8 mL/min).

ADVERSE REACTIONS

Ensure that the statement regarding the common adverse reactions is consistent with the information in the **FULL PRESCRIBING INFORMATION** under **6 ADVERSE REACTIONS**.

USE IN SPECIFIC POPULATIONS

Delete this section in the **HIGHLIGHTS** when there are no deviations to the use of the product in a specific population.

FULL PRESCRIBING INFORMATION: CONTENTS

Ensure that the **CONTENTS** is consistent with the **FULL PRESCRIBING INFORMATION**.

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

As stated above, the proposed indications statement is cumbersome and grammatically incorrect. For comprehension and readability, please revise. For example:

HEMGENIX is an adeno-associated virus vector-based gene therapy indicated to reduce the frequency of bleeding episodes (b) (4) in adults with Hemophilia B (congenital Factor IX deficiency) (b) (4) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

2 DOSAGE AND ADMINISTRATION

- There are multiple bolded subheadings. Avoid the use of bolding unless it is required by regulation. Underline or italics may be used for additional subheadings (use consistent style throughout).
- Avoid redundant information.
- Include the following required verbatim statement for parenteral products (21 CFR §201.57(c)(3)(iv)):

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

- In subheading 2.3, step 2 it states, “Use the diluted HEMGENIX solution as soon as possible.” While it is stated that the solution should not be stored beyond 24 hours after preparation, if there are data quantifying a change in safety and/or effectiveness over time, this should be used to revise this statement to be more specific, if possible. For example – “Use the diluted HEMGENIX solution within x period of time.”

5 WARNINGS AND PRECAUTIONS

In subsection 5.3, the statement “...both subject groups, with and without preexisting neutralizing anti-AAV5 antibodies, demonstrated an improved hemostatic protection compared to the standard of care...” is promotional in nature. Consider revising or removing.

6 ADVERSE REACTIONS

- Avoid use of internal company studies names and National Clinical Trial (NCT) numbers.
- In subsection 6.1, it is stated that “Infusion related reactions were mild to moderate in severity.” This is promotional in tone. The criteria for assigning these classifications should be clearly listed. Otherwise, this statement should be revised with more specific classifiers.

7 DRUG INTERACTIONS

Delete this section when there are no data.

10 OVERDOSAGE

This is not a required section and should be deleted when there are no data.

12 CLINICAL PHARMACOLOGY

- There are multiple bolded subheadings. Avoid the use of bolding unless it is required by regulation. Underline or italics may be used for additional subheadings (use consistent style throughout).
- Revise the mechanism of action section. Statements regarding mechanisms may be promotional. Statements such as “partially or completely ameliorates” lack clear quantifiable meaning.
- Avoid vague, non-quantifiable descriptors, such as ‘in general’, ‘almost,’ etc.

13 NONCLINICAL TOXICOLOGY

Include subsection 13.1 Carcinogenesis, Mutagenesis Impairment of Fertility. If there are no carcinogenicity data, then so state.

14 CLINICAL STUDIES

- Avoid the use of study names and numbers throughout this section. The study names and numbers greatly detract from the readability of this section.
 - For each subsection header, use italics or underline instead of bolding.
 - Avoid use of terms such as primary and secondary endpoint/objective. Describe only those endpoints that were statistically and clinically significant or demonstrated a meaningful lack of effect.
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17 PATIENT COUNSELING INFORMATION

- Reference to any appended FDA-approved patient labeling should appear directly beneath this section heading using the appropriate regulatory language.
- This section assists the healthcare provider in counseling the patient. It should be a list of major risks and how to manage or mitigate them. It should not be a relisting of every warning and precaution in the PI.
- Improve readability of this section by creating a parallel list in a logical order and avoiding long paragraphs. For example

Inform patients that

- Pre-infusion blood tests will be necessary to look for Factor IX inhibitors and pre-existing neutralizing anti-AAV5 antibodies. If these exist, the patient may not be a good candidate for HEMGENIX.
- Prior to HEMGENIX treatment, a liver ultrasound and elastography will be performed. Patients found to have pre-existing risk factors for hepatocellular carcinoma will be monitored annually in the 5 years following infusion.
- Infusion reactions can occur. Patients will be monitored during and for at least 3 hours following administration. If a reaction occurs, the infusion rate may be slowed or interrupted, then started at a slower rate.
- HEMGENIX can elevate certain liver enzymes. Weekly blood tests will be required to monitor for this for 3 months after treatment. Corticosteroid treatment may be necessary if this occurs.
- If post-infusion bleeding is not controlled or if bleeding returns, then blood tests will be performed to for Factor IX activity and neutralizing Factor IX inhibitors.
- Vector shedding in blood and semen can occur post-infusion. It is not known how long this will continue. Patients should not donate blood, organs, tissues, or cells for transplantation.

PACKAGE AND CONTAINER LABELS

The DNA double helix graphic to the left of the proprietary name is considered intervening matter and must be removed from container and carton labels.

If you have any questions regarding this review, please contact Benjamin S. Cyge, Consumer Safety Officer at (301) 796-4212.
