



**U.S. FOOD & DRUG
ADMINISTRATION**

Memorandum

DATE: November 13, 2023

TO: Linda Le, MBA, RPM, CBER/OTP/ORMRR/DRMRR2/RMSB2
Ashley Munchel, M.D., Clinical Reviewer, CBER/OTP/OCE/DCEH/BHB

FROM: Benjamin S. Cyge, Ph.D.
Consumer Safety Officer
Advertising and Promotional Labeling Branch (APLB)
Division of Case Management (DCM)
Office of Compliance and Biologics Quality (OCBQ)

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

SUBJECT: CASGEVY (exagamglogene autotemcel)
BLA: 125788/0
Sponsor: Bluebird Bio, Inc.

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

Submission Date: April 21, 2023

PDUFA Action Date: **December 20, 2023**

APLB Comments/Recommendations

This is a labeling review for BLA 125788, submitted by Bluebird Bio, Inc. for LYFGENIA (lovotibeglogene autotemcel) on April 21, 2023. LYFGENIA is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events.

The following APLB review addresses the proposed prescribing information, patient package insert, and package and container labels, submitted on April 21, 2023. Please note that the comments below, provided from a promotional and comprehension perspective, are not exhaustive. We recommend that the applicant consult the regulations (21 CFR §201.57, §610.61, §610.62, and §610.63) and associated labeling guidances (<https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>) to ensure that their edited draft labeling comports with the regulations.

GENERAL

- Use active voice and command language throughout the PI to increase 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.

HIGHLIGHTS

DOSAGE AND ADMINISTRATION

- Consider adding guidance on washout time after myeloablative conditioning. For example,
“Following myeloablative conditioning, allow a minimum of 48 hours of washout before LYFGENIA infusion.”
- Avoid use of trailing zeros.

ADVERSE REACTIONS

Consider rewording the phrase “diastolic blood pressure decreased” to “decrease in diastolic blood pressure” to enhance readability.

DRUG INTERACTIONS

The sentence “Do not take anti-retroviral medications or hydroxyurea for at least (b) (4) month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed” is confusing. Consider rewording and splitting up into more than one sentence to aid in comprehension.

FULL PRESCRIBING INFORMATION: CONTENTS

Ensure any changes in the **FULL PRESCRIBING INFORMATION** will also reflect in the **CONTENTS**.

FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

Ensure that the language and terminology between this section and the corresponding section in **HIGHLIGHTS** is consistent.

2 DOSAGE AND ADMINISTRATION

- Avoid the use of trailing zeros.
- Under section **2.2 Preparation Before LYFGENIA Infusion** clinicians are advised to discontinue erythropoietin, iron chelation, voxelotor, and crizanlizumab prior to stem cell collection and conditioning. These treatments are not listed as drug interactions or contraindications. Ensure that they are added to the appropriate sections, if necessary, and maintain consistency throughout the PI for safety guidance.
- Clinicians are advised to “perform screening for infectious diseases, specifically human immunodeficiency virus 1 & 2 (HIV-1/HIV-2) ...,” with no explanation of rationale or next steps. Consider providing explanation of rationale, or otherwise removing this sentence.
- It is stated that Granulocyte-colony stimulating factor (G-CSF) is not recommended for 21 days after LYFGENIA infusion; however, G-CSF is not listed as a contraindication. Ensure that there are no inconsistencies in safety guidance throughout the PI.

5 WARNINGS AND PRECAUTIONS

Consider revising or removing the sentence “patients with sickle cell disease have an increased risk of hematologic malignancy as compared to the general population due to stress on the hematopoietic system associated with the disease.” This sentence is promotional in the context of addressing the risk of hematologic malignancy in patients treated with LYFGENIA.

6 ADVERSE REACTIONS

Directly underneath the section header, state the most commonly reported adverse reactions with a cut-off frequency rate. The statement must be consistent with what is listed in the Adverse Reactions section of the **HIGHLIGHTS**.

8 USE IN SPECIFIC POPULATIONS

In subsection **8.3 Females and Males of Reproductive Potential** consider removing the sentence “advise patients of the risks associated with conditioning agents.” If it is deemed necessary to cross reference risks, they should be directly listed here, rather than referring the reader to look elsewhere.

12 CLINICAL PHARMACOLOGY

In subsection 12.1, the last two sentences pointing to lifelong improvement of disease symptoms are promotional. Please remove these sentences.

17 PATIENT COUNSELING INFORMATION

The advisement of hematologic malignancy is overly wordy. Only pertinent information is needed here. Consider revising to state the risk of malignancy and the precautions and monitoring that will be performed.

PATIENT PACKAGE INSERT

In the section “How will I get LYFGENIA” there are multiple references to the use of chemotherapy. This classification is too broad and can lead to confusion. Instead of *chemotherapy*, consider stating conditioning or mobilizing medicine, where applicable.

PACKAGE AND CONTAINER LABELS

The graphic under “lyfgenia” and above “Suspension for IV infusion” adversely affects the prominence of the proper name by drawing attention to the proprietary name. It also breaks up the product title by splitting the dosage form from the proper and proprietary names. Please remove this graphic from the product title.

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