



Memorandum

DATE: January 12, 2024

TO: Danielle Bauman, RPM, CBER/OTAT/DRPM/RPMB1
Muhammad Choudhry, M.D., Clinical Reviewer, CBER/OTAT/DCEPT
Kavita Natrajan, MD, Clinical Reviewer, CBER/OTAT/DCEPT

FROM: Lisa L. Stockbridge, Ph.D.
Branch Chief
Advertising and Promotional Labeling Branch (APLB)
Division of Case Management (DCM)
Office of Compliance and Biologics Quality (OCBQ)

SUBJECT: CASGEVY (exagamglogene autotemcel)
BLA: 125785/0
Sponsor: Vertex Pharmaceuticals, 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: March 31, 2023

PDUFA Action Date: **March 30, 2024**

APLB Comments/Recommendations

This is a labeling review for BLA 125785, submitted by Vertex Pharmaceuticals, Inc. for CASGEVY (exagamglogene autotemcel) on March 31, 2023. CASGEVY is a CRISPR/CAS9-

modified autologous CD34⁺ hematopoietic stem and progenitor cell (HSPC) cellular therapy indicated for the treatment of transfusion-dependent β -thalassemia (TDT) in patients 12 years and older.

The following APLB review addresses the proposed prescribing information, and patient package insert, submitted on December 18, 2023, and the proposed package and container labels, submitted on December 18, 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 the timeline between myeloablative conditioning and infusion. For example,

“CASGEVY must be administered between 48 hours and 7 days after the last dose of the myeloablative conditioning.”

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**.

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 matching.

2 DOSAGE AND ADMINISTRATION

- Avoid the use of vague and undefined language.
 - Under subsection **2.2 Preparation before CASGEVY infusion** the sentence “Maximize cell collection to obtain as many CD34⁺ cells as possible during each mobilization and apheresis cycle” is not followed by any protocol or guidelines on how to do so. Consider adding brief directions if they are necessary for proper procedure or removing the sentence if practice of medicine.
- For clarity, revise the sentence “Discontinue disease modifying therapies (e.g., hydroxyurea...” to include the name of the disease (SCD).
- Acronyms must be defined the first time they are used in the PI. G-CSF is not defined here.
- It is stated that granulocyte colony-stimulating factor (G-CSF) should not be administered for mobilization in patients with sickle cell disease. As CASGEVY is indicated only for patients with SCD, and mobilization is a necessary component of the protocol, consider adding G-CSF to the list of contraindications.
- Subsection **2.3 Administration** contains bolding to define the steps of administration. Avoid the use of bolding unless required by regulation. Consider using italics or underlining, and maintaining consistency with formatting used in the rest of the PI.
- The protocol for administration, especially step 1, “attaching the vial adapter and filter,” can be difficult to interpret without prior experience. Consider adding a picture or diagram to aid with comprehension.
- Consider providing preparation and administration instructions as defined steps in a logical order. Figures might assist in comprehension of the instructions.

4 CONTRAINDICATIONS

Consider removing the sentence “Contraindications to mobilization and myeloablative conditioning agents must be considered.” If it is deemed necessary to cross reference contraindications, they should be directly listed here, rather than referring the reader to look elsewhere.

5 WARNINGS AND PRECAUTIONS

Consider removing the sentence “Warnings and precautions to mobilization and myeloablative conditioning agents must be considered.” If it is deemed necessary to list warnings and precautions for these, they should be directly listed here rather than referring the reader to look elsewhere.

6 ADVERSE REACTIONS

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

7 DRUG INTERACTIONS

- This section must be consistent with the corresponding section in **HIGHLIGHTS**.
- Information directly under this heading and above a subsection heading may be lost in some stylesheets.

Consider removing the sentence “The drug-drug interaction of mobilization and myeloablative conditioning agents must be considered.” If it is deemed necessary to list such drug-drug interactions, they should be directly listed here rather than referring the reader to look elsewhere.

- Consider adding G-CSF, as it is suggested to be contraindicated in section **2 DOSAGE AND ADMINISTRATION**.

8 USE IN SPECIFIC POPULATIONS

Avoid use of internal study names and numbers.

12 CLINICAL PHARMACOLOGY

In subsection 12.1, the last sentence suggesting that the effects of CASGEVY are expected to be permanent is promotional in tone.

14 CLINICAL STUDIES

- It is unnecessary to use subsection numbers here, since there is only one subsection. .
- Avoid the use of study names and numbers throughout this section. The study names and numbers greatly detract from the readability of this section.

17 PATIENT COUNSELING INFORMATION

To enhance readability and comprehension, consider organizing and combining similar concepts in this section into two major bulleted subsections. For example:

Prior to treatment, advise patients of the following:

After treatment, advise patients of the following:

PATIENT PACKAGE INSERT

APLB has no comments on the patient package insert.

PACKAGE AND CONTAINER LABELS

APLB has no comments on the package and container labels.

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

Application #:	125785/0
Firm Name:	Vertex Pharmaceuticals, Inc.
Document Type:	LR

Drafted:	B. Cyge	11/02/2023
Revised:	L. Stockbridge	1/12/2024
Final:	L. Stockbridge	1/12/2024

Bcc:

HFM-602 APLB Historical File
HFM-602 APLB Chronological File

Concurrence Box:

Mail Code or Office	Name	Date/Approval
HFM-602	Lisa Stockbridge	
Lock Document	Danielle Bauman	