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## Memorandum

**DATE:** February 3, 2024

**TO:** Monique Cortez, RPM, CBER/OTAT/DRPM/RPMBI  
Avanti Golikeri, M.D., Clinical Reviewer, CBER/OTAT/DCEPT

**FROM:** Benjamin S. Cyge, Ph.D.  
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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: LENMELDY (atidarsagene autotemcel)**  
**BLA: 125758/0**  
Sponsor: Orchard Therapeutics

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## 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: July 19, 2023

PDUFA Action Date: March 18, 2024

## **APLB Comments/Recommendations**

This is a labeling review for BLA 125758, submitted by Orchard Therapeutics for LENMELDY (atidarsagene autotemcel) on July 19, 2023. LENMELDY is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

The following APLB review addresses the proposed prescribing information, patient package insert, and the proposed package and container labels, submitted on July 19, 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.
- Avoid the use of study names and numbers to ensure better readability.

### **HIGHLIGHTS**

#### **DOSAGE AND ADMINISTRATION**

- Consider adding the timeline between myeloablative conditioning and infusion. For example,  

“LENMELDY must be administered via intravenous infusion by gravity flow within 30 minutes of thawing.”
- Avoid the use of trailing zeros in dosage to avoid dosing mistakes.

#### **DOSAGE FORMS AND STRENGTHS\**

Avoid the use of trailing zeros in dosage to avoid dosing mistakes.

#### **FULL PRESCRIBING INFORMATION: CONTENTS**

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

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## **FULL PRESCRIBING INFORMATION**

### **2 DOSAGE AND ADMINISTRATION**

- Avoid the use of trailing zeros in dosage to avoid dosing mistakes.
- In subsection **2.2 Preparation before LENMELDY Infusion**, the statement “Refer to the prescribing information for the mobilization agent(s) and the myeloablative conditioning agent(s) prior to treatment” should be removed. If there is pertinent information that is necessary for proper administration of the protocol, it should be added directly here. The reader should not be expected to obtain this information from another products prescribing information.
- Under subsection “Preparation of LENMELDY for Infusion” more details on thawing and infusion should be listed in the first paragraph. While these details are outlined later, the current sentence, “Confirm the infusion time in advance and adjust the start time of LENMELDY thaw such that it will be available for infusion when the patient and healthcare providers are ready,” is too vague.
- In subsection **2.3 Administration** there is an abrupt switch between bullets and numbering. For consistency, consider adding this information within the numbered steps, and italicize for emphasis, where necessary.

### **3 DOSAGE FORMS AND STRENGTHS**

Avoid the use of trailing zeros in dosage to avoid dosing mistakes.

### **5 WARNINGS AND PRECAUTIONS**

Consider removing the last sentence of the first paragraph in **subsection 5.1 Delayed Platelet Engraftment**, which reads, “During the OLT-200 clinical development program, 10% of patients had not achieved platelet engraftment...” In this section of the PI, it is sufficient to simply state that there is a risk of this, and it has happened. Reference to the clinical data section can be added to direct the reader to the details of this.

### **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**.
  - Subsection 6.1 only should include adverse reactions. An *adverse event* may not have an association, or reasonably likely association, with the product, and this distinction can be used in promotion.
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## 7 DRUG INTERACTIONS

Consider adding a brief statement referencing the advised avoidance of anti-retrovirals directly under the section header.

## 8 USE IN SPECIFIC POPULATIONS

- Consider revising **subsection 8.1 Pregnancy** to add more details. For example:

“There are no clinical data from the use of LENMELDY in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with LENMELDY to assess whether it can cause fetal harm when administered to a pregnant woman. LENMELDY must not be administered during pregnancy because of the risk associated with myeloablative conditioning. Pregnancy after LENMELDY infusion should be discussed with the treating physician.”

- **Subsection 8.2 Lactation** is not sufficiently detailed. Consider revising, as below:

“There are no data on the presence of LENMELDY in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential risks associated with myeloablative conditioning, breast-feeding should be discontinued during conditioning. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for LENMELDY and any potential adverse effects on the breastfed child from LENMELDY or from the underlying maternal condition. Breast-feeding after LENMELDY infusion should be discussed with the treating physician.”

- As the PI is currently written, there is a contradiction between **subsections 8.1 and 8.3**. **Subsection 8.1** advises to consider the risks associated with conditioning and pregnancy, while **subsection 8.3** clearly states that a negative serum pregnancy test must be confirmed prior to the start of mobilization. Consider revising **subsection 8.1**, as above to maintain consistency in advising against the administration of LENMELDY in pregnant women.
- Under subheading “Contraception” it states, “Consult the Prescribing Information of the mobilization and conditioning agents for information on the need for effective contraception.” Avoid advising readers to refer to PIs of other products. As the protocol for LENMELDY uses specific agents for mobilization and conditioning, if this information is important enough to include, it is advised that details be added to this PI.

## 12 CLINICAL PHARMACOLOGY

- In **subsection 12.1**, the last sentence reads, “Functional ARSA enzyme can play role in breakdown of sulfatides.” This statement is both vague and potentially promotional in tone. Only statements of clear fact should be included in the description of the mechanism of action.
- The last sentence in **subsection 12.2 Pharmacodynamics** contains the statement, “...providing indirect evidence that gene-corrected cells have migrated to the CNS and

are producing and secreting functional ARSA enzyme.” Remove or revise this statement, as it is vague and promotional in tone.

## **14 CLINICAL STUDIES**

- For subsection headers, use italics or underline instead of bolding.
- Avoid the use of study names and numbers throughout this section. The study names and numbers greatly detract from the readability of this section. Also, the end user rarely has access to the study.

## **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**

- List the specific treatment used, rather than referring to “chemotherapy.” This is persistent throughout the package insert.
- In the second bullet under “What is the most important information I should know about LENMELDY, remove the words “the only” from the statement “The only adverse event related to LENMELDY reported up to 3 months after treatment...”
- As mobilization and myeloablative conditioning are necessary components to the protocol of LENMELDY treatment, it is advisable that the separation between “LENMELDY” associated, and non-LENMELDY associated events be removed. It is not acceptable to abdicate responsibility for some adverse events, when all patients treated with LENMELDY will be subject to these risks.
- The section “What are the possible or reasonably likely side effects of treatment with LENMELDY?” is word for word verbatim with the section “What is the most important information I should know about LENMELDY.” This section should be revised as is advised in the above reference to the first section. The section “What is the most important information I should know about LENMELDY” is meant to be a brief overview of what LENMELDY treatment is, and which symptoms to look for and when to seek assistance from a healthcare provider.

### **PACKAGE AND CONTAINER LABELS**

Revise the product title to remove the image in front of the proprietary name, LENMELDY. This constitutes intervening matter between the proper and proprietary names, which adversely affects the prominence of the proper name.

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

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Concur w/rev:	L. Stockbridge	2/3/2024
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Bcc:

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

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