



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

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## Memorandum

**DATE:** August 10, 2022

**TO:** Julia Wright, MHA, RN, RPM, CBER/OTAT/DRPM  
Colleen Caldwell, MS, MPH, RPM, CBER/OTAT/DRPM  
Anna Kwilas, Ph.D., Committee Chair, CBER/OTAT/DCGT  
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Shelby Elenburg, 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: SKYSONA (elivaldogene antotemcel)**  
**BLA: 125755/0**  
Sponsor: Bluebird Bio, Inc.

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## 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: October 18, 2021

PDUFA Action Date: September 16, 2022

## APLB Comments/Recommendations

This is a labeling review for BLA 125755, submitted by Bluebird Bio, Inc. for SKYSONA (elivaldogene autotemcel) on October 18, 2021. SKYSONA is an *ABCD1* gene addition therapy indicated for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy (CALD) who do not have an available and willing human leukocyte antigen (HLA)-matched sibling hematopoietic stem cell (HSC) donor

APLB reviewed the draft prescribing information (PI), patient package insert (PPI), package, and container labels dated October 18, 2021. The following comments are from a promotional and comprehension perspective.

### 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 infusion rate to this section. For example,

“Administer each infusion bag of SKYSONA via intravenous infusion over a period of less than 60 minutes.”

#### 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

#### 2 DOSAGE AND ADMINISTRATION

- Bold the statements directly beneath the section heading:

**For autologous use only. For intravenous use only.**

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- 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.
- The PI should provide sufficient information for the safe and effective use of this product. Avoid instructing the reader to look elsewhere for additional information. Therefore, delete or revise the statement “Consult prescribing information for the conditioning agent(s) prior to treatment.” If it is necessary to provide information on the conditioning agent(s), specify those agents here.
- To enhance readability and comprehension, we recommend revising section 2. Furthermore, revise subsection 2.2 to provide information on patient and product preparation before product infusion. Therefore, the administration section will be subsection 2.3. Group related information and combine under the appropriate subsection headers. For sub-subsection headers, use italics or underline for emphasis. For example,

## **2.1 Dose**

## **2.2 Preparation Before SKYSONA Infusion or Preparing the Patient for Infusion**

*Mobilization and Apheresis*

*Myeloablative and lymphodepleting conditioning*

*Receipt and Storage of SKYSONA*

*Preparation of SKYSONA for Infusion*

## **2.3 Administration**

*Prior to SKYSONA Infusion*

*After SKYSONA Infusion*

## **5 WARNINGS AND PRECAUTIONS**

Consider revising the statement “In the event of concerning clonal expansion or predominance...,” to specify the parameters defining “concerning.” As is, this statement is vague.

## **6 ADVERSE REACTIONS**

Directly following the section heading, and before subsection 6.1 Clinical Trials Experience:

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- Include a list of the most frequently occurring adverse reactions, along with the criteria used to determine inclusion (e.g., incidence rate greater than x%).
- Include a statement about serious adverse reaction(s) (i.e., caused death or discontinuation), even if not frequent.
- All of the above statements must be consistent with the ADVERSE REACTIONS section in the HIGHLIGHTS.

## 8 USE IN SPECIFIC POPULATIONS

- In subsection 8.1, the following statement should be moved directly under the subheading:

“It is not known whether SKYSONA has the potential to be transferred to the fetus. Therefore, SKYSONA should not be used in women who are pregnant, and pregnancy after SKYSONA infusion should be discussed with the treating physician.”
- In subsection 8.2, the sentence stating that SKYSONA is not recommended for women who are breastfeeding should be the first sentence in the paragraph.
- Subsection **8.5 Geriatric Use** is a required subsection and must be included with appropriate regulatory language. (See 21 CFR §201.57(c)(9)(v))

## 11 DESCRIPTION

Add the proper name of the product, elivaldogene autotemcel, to the description.

## 12 CLINICAL PHARMACOLOGY

- Speculation on mechanism of action is considered promotional, and therefore, the following should be removed:

“Although the mechanism of action is not fully understood, it is hypothesized that after SKYSONA infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes (CD14+) that migrate to the brain where they are believed to further differentiate into macrophages and cerebral microglia that can produce functional ALDP. The functional ALDP can then participate in the local degradation of very long chain fatty acids (VLCFAs) in the brain, which in turn can stabilize the disease by preventing or slowing further inflammation and demyelination.”
- In subsection 12.3, consider revising the statement “The nature of SKYSONA is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable,” with elaboration as to why this is the case. It is currently too vague.

## 14 CLINICAL STUDIES

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- 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. Describe only those endpoints that were statistically and clinically significant or demonstrated a meaningful lack of effect.
- Delete or revise the sentence that begins “SKYSONA demonstrated an early benefit compared to allo-HSCT from an unmatched donor,” as it is promotional in tone.

### **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.

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Application #:	125755/0
Firm Name:	Bluebird Bio, Inc.
Document Type:	LR

Drafted:	B. Cyge 8/8/22
Concur w/rev:	S. Saini 8/8/22
Concur w/rev:	L. Stockbridge 8/8/22
Final:	B. Cyge 8/10/22

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