



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

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## Memorandum

**DATE:** August 1, 2022

**TO:** Cara Pardon, RPM, CBER/OTAT/DRPM/RPMBI  
Jakob Reiser, Ph.D., Committee Chair, CBER/OTAT/DCGT/GTIB  
Karl Kassamon, M.D., Clinical Reviewer, CBER/OTAT/DCEPT

**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: ZYNTGLO (betibeglogene autotemcel)**  
**BLA: 125717/0**  
Sponsor: Bluebird Bio, Inc.

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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: September 20, 2021

PDUFA Action Date: **August 20, 2022**

## **APLB Comments/Recommendations**

This is a labeling review for BLA 125717, submitted by Bluebird Bio, Inc. for ZYNTGLO (betibeglogene autotemcel) on September 20, 2021. ZYNTGLO is a  $\beta^{A-T87Q}$ -globin gene addition therapy indicated for the treatment of patients with  $\beta$ -thalassemia who require regular red blood cell (RBC) transfusions.

The following APLB review addresses the proposed prescribing information, patient package insert, and the proposed package and container labels, submitted on September 20, 2021. 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 research terminology as it decreases readability. For example, Phase 1/2, Phase 3.
- 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 ZYNTGLO via intravenous infusion over a period of less than 30 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**

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## 2 DOSAGE AND ADMINISTRATION

- Avoid the use of bolding unless it is required by regulation.
- 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 “Refer to the prescribing information for the mobilization agent(s) and the myeloablative conditioning agents(s) prior to treatment.” If it is necessary to provide information on the mobilization agent(s) or myeloablative conditioning agent(s), specify those agents here.
- To enhance readability and comprehension, we recommend revising subsection 2.2 to provide information on patient and product preparation before product infusion. Therefore, the administration section will all 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 ZYNTGLO Infusion or Preparing the Patient for Infusion

*Mobilization and Apheresis*

*Myeloablative conditioning*

*Receipt and Storage of ZYNTGLO*

*Preparation of ZYNTGLO for Infusion*

### 2.3 Administration

*Prior to ZYNTGLO Infusion*

*After ZYNTGLO Infusion*

## 5 WARNINGS AND PRECAUTIONS

In subsection 5.3, delete the second sentence “There are no reports of insertional oncogenesis associated with ZYNTGLO or BB305LVV.” This sentence minimizes the first sentence stating the risk for lentiviral vector mediated insertional oncogenesis.

## 6 ADVERSE REACTIONS

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- Directly underneath the section header, state the most commonly reported adverse reaction rates with a cut-off frequency rate.
- Subsection 6.1 is entitled “Clinical Trials Experience” not “Clinical Studies Experience.”
- Revise the regulatory wording underneath the subsection header 6.1 to the follow statement:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

- In the tables, round the percentages to a whole integer.

## 12 CLINICAL PHARMACOLOGY

In subsection 12.1, the last sentence regarding the effects of ZYNTÉGLO are expected to be life-long is promotional in tone.

## 14 CLINICAL STUDIES

- It is unnecessary to use subsection numbers here especially when there's only one subsection.
- For each subsection header, 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.
- Delete the statement regarding exploratory analyses suggesting that the product improves erythropoiesis. This is considered promotional.

## 17 PATIENT COUNSELING INFORMATION

This section is densely worded and disorganized. 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**

Revise the section titled “How will I get ZYNTÉGLO?” This section is extremely wordy and contains lengthy explanations of the process. Patients may likely skip over or miss important

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information when it is in dense paragraphs. Simplify this section by providing just 1-2 sentences under each step.

## **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.