U.S. FOOD & DRUG ADMINISTRATION

## Memorandum

**DATE:** July 18, 2017

**TO:** Xiaobin (Victor) Lu, Ph.D., Chairperson
CBER/OTAT/DCGT/GTB

Erica Giordano, RPM
CBER/OTAT/DRPM/RPMBI

**FROM**: Dana C. Jones, CSO
CBER / OCBQ/DCM/APLB

**THROUGH:** Lisa L. Stockbridge, Ph.D.
CBER / OCBQ/DCM/APLB

**SUBJECT:** Labeling Review
**KYMRIAH (tisagenlecleucel)**
**BLA 125646/0**
Sponsor: Novartis Pharmaceuticals Corp.

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**Background:** The sponsor submitted:

X New Approval
_____ Changes Being Effected (CBE) supplement
_____ Prior Approval Supplement (PAS) Amendment
_____ Major Amendment

Submission contains:
X Prescribing Information (PI)
_____ Patient Package Insert (PPI)
X Package and/or container labels
X Other (Medication Guide)

Submission Date: February 2, 2017

PDUFA Action Date: October 3, 2017

## APLB Comments/Recommendations

On February 2, 2017, Novartis Pharmaceuticals Corporation submitted an original Biologics License Application (BLA) for KYMRIAH (tisagenlecleucel) a CD19-directed genetically-modified autologous immunotherapy indicated in combination with lymphodepleting chemotherapy for the treatment of pediatric and young adult patients 3-25 years of age with relapse or refractory B-cell pre-cursor acute lymphoblastic leukemia (ALL).

On April 13, 2017, APLB recommended that the proposed proprietary name, KYMRIAH, be found acceptable.

APLB concurs with the revisions made by the review team. The following comments and recommendations are in addition to all changes already made from a promotional and comprehension perspective.

**GENERAL**

- Upon approval ensure that the 4-digit year is entered for the "Initial U.S. Approval."
- Use active voice when possible.
- Use command language for instructions when possible.
- Provide full text with the first use of an acronym.
- Avoid use of bold print unless required by regulation.
- Avoid overuse of bullets, as it desensitizes the reader to important information and reduces readability. Only bullet when there are two or more disparate concepts.
- Remove date from the end of the Full Prescribing Information (FPI). The date is required at the end of the **HIGHLIGHTS** section, and should not appear in both places.

**HIGHLIGHTS**

- The **HIGHLIGHTS** should not exceed ½ page. Use command language and summary statements throughout, especially in **WARNINGS AND PRECAUTIONS**, which will remedy this concern.

- The **DOSAGE AND ADMINISTRATION** section should include the route of administration with a bolded, sentence case phrase placed directly beneath the section heading. Please add the following route of administration:

**For intravenous infusion only.**

  - Please provide the full text for the acronym CAR 19 upon first use.
  - Please correct the following typographical error:

Verify the patient's ~~identify~~ identity prior to infusion (2.1)

- The **WARNINGS AND PRECAUTIONS** should be listed in decreasing order of severity and public health significance.

- The warning concerning fetal risk belongs under **USE IN SPECIFIC POPULATIONS**.

## TABLE OF CONTENTS (TOC)

Ensure that the **TOC** aligns with the section headings of the **FULL PRESCRIBING INFORMATION (FPI)** and has the correct numbering. Note that not every subsection is hyperlinked from the TOC. (See 21 CFR §201.56(d)(1)):

**BOXED WARNING**
**1 INDICATIONS AND USAGE**
**2 DOSAGE AND ADMINISTRATION**
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
**5 WARNINGS AND PRECAUTIONS**
**6 ADVERSE REACTIONS**
**8 USE IN SPECIFIC POPULATIONS**
**8.1 Pregnancy**
**8.2 Lactation**
**8.3 Females and Males of Reproductive Potential**
**8.4 Pediatric Use**
**8.5 Geriatric Use**
**11 DESCRIPTION**
**12 CLINICAL PHARMACOLOGY**
**12.1 Mechanism of Action**
**12.2 Pharmacodynamics**
**12.3 Pharmacokinetics**
**12.4 Microbiology**
**12.5 Pharmacogenomics**
**13 NONCLINICAL TOXICOLOGY**
**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
**13.2 Animal Toxicology and/or Pharmacology**
**14 CLINICAL STUDIES**
**16 HOW SUPPLIED/STORAGE AND HANDLING**
**17 PATIENT COUNSELING INFORMATION**

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- Please remove the paragraph under 2.2 Administration. The **TABLE OF CONTENTS** should contain only the headings of sections (and some required subsections) within the FPI. All other text should be removed.

## FULL PRESCRIBING INFORMATION (FPI)

### BOX WARNING

The BOX WARNING heading should be placed inside the box, centered and in uppercase letters. Please center the heading and include a section cross-reference for the third bulleted point. (e.g., CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS).

## 2 DOSAGE AND ADMINISTRATION

- Please include the route of administration directly beneath the heading **DOSAGE AND ADMINISTRATION**, we recommend using the bolded statement:

  **For intravenous infusion only.**

- Revise this section to a logical sequence of dose, preparation, administration, and managing expected adverse reactions specific to administration. Adverse reaction information should be cross referenced to **WARNINGS AND PRECAUTIONS**.

- Please change the **2.1 Recommended Dosage** subsection title to the following:

  **2.1 Dose**

- Provide basic dosing information first, followed by other information relevant to dosage calculation. The sequence of information should reflect the relative importance of the information presented.

- Please quantify the statement “until resolved.”

- For readability, presenting the information as numeric steps. For example:

  **Step 1 Confirm Patient Identity**
  **Step 2 Inspect and Thaw Infusion Bag(s)**

## 3 DOSAGE FORMS AND STRENGTHS

Please include a statement indicating that the final dosage will be printed on the patient specific infusion bag(s).

## 4 CONTRAINDICATIONS

Please cross-reference section **11 DESCRIPTION** for the product components.

## 5 WARNINGS AND PRECAUTIONS

The warning concerning fetal risk belongs in **USE IN SPECIFIC POPULATIONS**.

## 6 ADVERSE REACTIONS

- Include the statement of the most common adverse reactions, with their cutoff frequency, directly beneath the heading of section **6 ADVERSE REACTIONS** section (before subsection 6.1).

- A hyperlink implies that there is greater detail elsewhere. For impact and readability, revise the phrase introducing the hyperlinks to the serious adverse reactions to:

  Serious adverse reactions for KYMRIAH include the following:

## 7 DRUG INTERACTIONS

This section is not required and should be deleted when there are no data**.**

## 8 USE IN SPECIFIC POPULATIONS

- Revise subsections 8.1, 8.2, and 8.3 to conform to the new Pregnancy and Lactation Labeling Rule (PLLR). (See *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*)

- The first five subsections are reserved. Subsections 8.1, 8.2, 8.4, and 8.5 are required. Additional subsection topics must start at 8.6:

  **8.1 Pregnancy**
  **8.2 Lactation**
  **8.3 Females and Males of Reproductive Potential**
  **8.4 Pediatric Use**
  **8.5 Geriatric Use**
  **8.n [next specific population]**

- Do not include additional subsections when there are no data (e.g., Renal and Hepatic Impairment, Active CNS Leukemia).

- Please correct the font and spacing in this section.

## 10 OVERDOSAGE

This section is not required and should be deleted if no human data is available.

## 11 DESCRIPTION

Please include the product's proper name as well as the proprietary name in this section.

KYMRIAH (tisagenlecleucel)

## 12 CLINICAL PHARMACOLOGY

- Subsection **12.2 Pharmacodynamics** is a required section. Please include a description of any biochemical or physiologic pharmacologic effects of the cell therapy or active metabolites, with respect to its clinical effect or to its adverse reactions or toxicity, if available.

- To improve readability in subsections, consider using tables rather than lengthy paragraphs to organize information.

## 14 CLINICAL STUDIES

- It is not necessary to subsection this section.

- Refrain from research terminology, such as: *pivotal, Phase II*, and *primary endpoint*.

- Remove study numbers. (There only is one study in the PI at this time.).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

- Overuse of bold font may lead to loss of readability.

- It is not necessary to use subheadings in a short section.

- Include the NDC code.

- Refrain from including practice of medicine.

## MEDICATION GUIDE

- The Medication Guide is a strictly formatted document with required regulatory language. Revise the proposed "Medication Guide" to be consistent with the regulations. (See 21 §CFR 208.20) In addition, please refer to the *Guidance: Medication Guides-Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* for more information on how to revise this section.

- Use active voice and plain language to enhance readability.

- Cross-referencing within the MedGuide is discouraged, as it reduces the readability and comprehension of the MedGuide.

- Throughout the Medication Guide the term w*hite blood cells* and *immune cells* are used interchangeably, for consistency and clarity, please use one term to describe the cells.

## CONTAINER LABEL

- Include the correct proper named as well as proprietary name.

**KYMRIAH (tisagenlecleucel)**

- Verify the accuracy of the NDC number.
- Include the telephone number.

If you have any questions regarding this review please contact Dana C. Jones, Consumer Safety Officer at 240-402-9012.