



Memorandum

DATE: August 11, 2017

TO: Michael Kennedy, Chairperson
CBER/OTAT/DCEPT/GMBI

Jiahua Qian, RPM
CBER/OTAT/DRPM/RPMBI

FROM: Alpita Popat, PharmD, MBA
CBER / OCBQ/DCM/APLB

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

SUBJECT: Labeling Review
KEDRAB [Rabies Immune Globulin (Human)]
BLA 125613/0
Sponsor: Kamada Ltd.

Background: The sponsor submitted:

New Approval
 Changes Being Effectuated (CBE) supplement
 Prior Approval Supplement (PAS) Amendment
 Major Amendment

Submission contains:

Prescribing Information (PI)
 Patient Package Insert (PPI)
 Package and/or container labels
 Other (IFU)

Submission Date: August 29, 2016

PDUFA Action Date: August 29, 2017

APLB Comments/Recommendations

On August 29, 2016, Kamada, Ltd. (Kamada) submitted a Biologics License Application (BLA) for KEDRAB [Rabies Immune Globulin (Human)]. KEDRAB is indicated for passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with a rabies vaccine.

On November 1, 2016, APLB recommended that the proposed proprietary name, KEDRAB, be found acceptable.

APLB reviewed the proposed labeling (submitted on April 26, 2017) and carton/container labels (submitted on August 29, 2016). The following comments are from a promotional and comprehension perspective.

Overall

- Please delete the periods between the section numbers and section titles throughout the **FULL PRESCRIBING INFORMATION (FPI)**.
- The FPI switches between the terms “patients” and “individuals.” This reduces overall readability and comprehension. Please pick one term and use this term consistently throughout the labeling.
- Use command language wherever possible.
- Please refer to product by its name, KEDRAB, not the abbreviation HRIG.
- In the **6 ADVERSE REACTIONS**, **12 CLINICAL PHARMACOLOGY**, and **14 CLINICAL STUDIES**, please simply describe the clinically significant results of the clinical trial, including overall exposure, demographics of exposed population, designs of trial (including the name of the comparator HRIG), and any critical exclusion from the safety database. When doing so, avoid using terms such as Phase 1, Phase 2, Phase 3, primary endpoint, and secondary endpoint.

HIGHLIGHTS

- The administration directive, located beneath the **DOSAGE AND ADMINISTRATION** heading, should be bolded: **(b) (4)**.
- In the second **DOSAGE AND ADMINISTRATION** bullet, please refer to the product by its name, KEDRAB.

FULL PRESCRIBING INFORMATION: CONTENTS

- Ensure that the **CONTENTS** align with the sections and subsections of the **FULL PRESCRIBING INFORMATION**.
- The **CONTENTS** should not be italics. Please remove this formatting.
- Please fix the subsection numbers for **6 ADVERSE REACTIONS** and **8 USE IN SPECIFIC POPULATIONS** section. The subsection numbers are pre-assigned for the subsections listed.

FULL PRESCRIBING INFORMATION (FPI)

2 DOSAGE AND ADMINISTRATION

Only the route of administration with a bolded font should be located beneath the **DOSAGE AND ADMINISTRATION** heading. Please move the remaining bullets to one of the other subsections.

2.2 Administration

The last two sections are considered practice of medicine and do not belong in the prescribing information.

4 CONTRAINDICATIONS

Per the regulations, this section must state “None.” if there are no contraindications. Please delete the current explanatory statement, as it detracts from the readability of the important information.

5 WARNINGS AND PRECAUTIONS

- The first bullet in the **5.2 Hypersensitivity** subsection, *True hypersensitivity reactions are rare*, minimizes the risk associated with KEDRAB. Similarly, the phrase, “rarely, HRIG can induce a fall in blood pressure...” minimizes the risk association with KEDRAB.
- In subsection 5.3, delete the directive that includes the phrase, “use care,” as this is detailed in another bullet in this subsection (also see next comment).
- The terms and phrases “rarely,” “with caution,” and “use care” are considered vague and minimize the adverse reactions associated with KEDRAB. Please delete these phrases from this section.

6 ADVERSE REACTIONS

- Directly beneath the heading **6 ADVERSE REACTIONS**, include the list of the most frequently occurring adverse reactions, along with the criteria used to determine inclusion (e.g., incidence rate greater than x%). This is the same statement that is found in the HIGHLIGHTS.
- In the **6.1 Clinical Trials Experience** subsection, the statement “*No deaths or serious adverse reactions occurred in the Phase 2/3 study, or in any study of KEDRAB*” minimizes the risks associated with KEDRAB. We recommend deleting the statement from this section.
- The **6.2 Postmarketing Experience** section is not required since there are no adverse reactions to report. The current statement minimizes the potential risks associated with KEDRAB and is considered promotional in tone.

8 USE IN SPECIFIC POPULATIONS

- Revise subsections titles for 8.3, 8.4, and 8.5 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 subsection headings should be the following:

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential (Omit)
- 8.4 Pediatric Use
- 8.5 Geriatric Use

- The statement, “KEDRAB should be given to a pregnant woman only if clearly needed” (**8.1 Pregnancy** subsection) is not recommended because it is not considered informative and not required. We recommend deleting this statement. Please refer to *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* for recommended language in this subsection.

11 DESCRIPTION

When describing lack of latex content, the regulatory language is “not made with natural rubber latex.” Please revise the statement, "made without the addition or use of latex."

13 NONCLINICAL TOXICOLOGY

In the absence of data, the **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection should be deleted. It is not required.

16 HOW SUPPLIED/STORAGE AND HANDLING

Use bullets or a table for the information under the section heading. This will increase readability.

PACKAGE AND CONTAINER LABEL

APLB has no comments on the package or container label.