NDA 214916

NDA APPROVAL

Cara Therapeutics, Inc.
Attention: Edward Liao, PharmD
Head of Regulatory Affairs
4 Stamford Plaza
107 Elm Street, 9th FL
Stamford, CT 06902

Dear Dr. Liao:

Please refer to your new drug application (NDA) received December 23, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Korsuva (difelikefalin) injection, 65 mcg/1.3mL.

This NDA provides for the use of Korsuva (difelikefalin) injection for the treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis (HD).

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214916** Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Korsuva (difelikefalin) injection, 65 mcg/1.3mL shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for Korsuva was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable based on data collected in pediatric patients with pruritus undergoing hemodialysis, ages 8 to 17 years and 11 months. Per the data, the number of pediatric patients undergoing hemodialysis who have CKD-aP is very small and pruritus is of very mild intensity, which rarely requires systemic therapy.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request additional pharmacovigilance activities to monitor the safety of Korsuva beyond routine pharmacovigilance. Provide the following in each quarterly periodic report for the first 3 years post-approval, then annually thereafter:

A summary, assessment, and listing of cases of the following serious adverse events of interest: 1) accidents and injuries, 2) respiratory failure, and 3) fatal arrhythmias in your global safety system from the time of approval through the end of the time period retrieved by, at minimum, using the following Medical Dictionary for Regulatory Activities (MedDRA) terminologies:

- Standardised MedDRA Queries (SMQs)
  - *Accidents and injuries (SMQ) Broad search)*
  - *Respiratory failure (Narrow search)*
  - *Arrhythmia related investigations, signs and symptoms*
  - *Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)*

- Preferred Terms (PTs)
  - *Altered states of consciousness*
  - *Balance disorder*
  - *Coma*
  - *Disorientation*
  - *Drug interaction*
  - *Gait disturbance*
  - *Hypersomnia*
  - *Mental status changes*
  - *Somnolence*

The summary and line listing of cases should include and be stratified by, where feasible, the following variables:

- Total number of cases of each adverse event of interest by time period and cumulative since approval

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

- Patient outcome
    - Fatal: (for all serious adverse events of interest)
        - Cause of death
    - Non-fatal (for accidents/injuries and respiratory failure)
        - Admitted to the hospital
        - Required medical interventions but not hospitalized (i.e., visit to the emergency room, visit to the clinician, pharmacologic or surgical intervention provided)
- Age (Mean, Range)
- Sex
- Indication for Korsuva
- Dosage of Korsuva
- Concurrent and past medical history, past surgical history
- Concomitant drugs [list all, including prescription and over-the-counter medications (indication, dosage), herbal, and illicit substances]
- Onset of serious adverse event of interest after Korsuva initiation with concomitant centrally-acting depressant(s) or pro-arrhythmic drug(s) (Mean, Range)
- Onset of serious adverse event of interest after initiating opioid centrally-acting depressant(s) or pro-arrhythmic drug(s) with concomitant Korsuva (Mean, Range)
- Action taken with Korsuva and centrally-acting depressant(s) or pro-arrhythmic drug(s) (i.e., continued or discontinued treatment)
- Dechallenge, Rechallenge
    - Korsuva
    - Centrally-acting depressant(s)
    - Pro-arrhythmic drug(s)

In your assessment, discuss the role of drug interactions between Korsuva and centrally-acting depressant(s) or pro-arrhythmic drug(s).

In addition to the summary and assessment in each periodic report, provide the above data, including the respective manufacturer control number for each case, in .xlsx format. As required under 21 CFR 314.80, you should report each adverse drug experience that is both serious and unexpected to the FDA within 15 days from initial receipt of the information (i.e., expedited reporting). As such, we request that you report each case of serious adverse events of interest to the FDA within 15 days from initial receipt of the information (i.e., expedited reporting). Every effort should be made to obtain thorough and complete follow-up of events related to the serious adverse events of interest, including making every effort to obtain results from specialist consults (e.g., cardiology, nephrology, neurology, pain management, psychiatry), assessments, or evaluations of patients with any events related to the adverse events of interest. The clinical information collected in this manner will enhance the quality of adverse event reports submitted to FDA and facilitate our assessment of these reports.

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jennifer Harmon, Regulatory Project Manager, at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE G BEITZ
08/23/2021 12:43:00 PM