



BLA 761094

BLA APPROVAL

Dompé farmaceutici S.p.A.
c/o Creative Regulatory Solutions, LLC
Attention: Robert J. McCormack, Ph.D.
U.S. Agent
14 Edinburgh Drive
Randolph, NJ 07869

Dear Dr. McCormack:

Please refer to your Biologics License Application (BLA) dated December 22, 2017, received December 22, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL).

LICENSING

We have approved your BLA for OXERVATE (cenegermin-bkbj) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, OXERVATE under your existing Department of Health and Human Services U.S. License No. 2074 which is indicated for treatment of neurotrophic keratitis.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture cenegermin-bkbj drug substance at Dompé farmaceutici S.p.A. in L'Aquila, Abruzzo, Italy. The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4) Italy. You may label your product with the proprietary name, OXERVATE, and market it as a topical ophthalmic solution.

DATING PERIOD

The dating period for OXERVATE shall be 12 months from the date of manufacture when stored at (b) (4) °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4).

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and/or drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of OXERVATE to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of OXERVATE, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

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 text.

We note that your August 9, 2018, submission includes final printed labeling (FPL) for your prescribing information, patient package insert, instructions for use. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, instructions for use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CONTAINER LABELS

We acknowledge your August 9, 2018, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for cenegermin-bkbj was not referred to an FDA advisory committee because the application did not raise significant new safety or new efficacy issues. Complete clearing of the corneal surface is a well-established clinical endpoint. The observed and/or reported adverse

events were consistent with the disease and/or are commonly evaluated in clinical trials of ocular surface conditions.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, PREA requirements are inapplicable; however, we note that the product is being approved for use in pediatric patients two years of age and older.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1. To conduct a clinical study to determine the extent of systemic exposure to cenegermin-bkbj following repeated topical ocular dosing of the final to-be-marketed formulation of OXERVATE containing methionine.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2019

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2. To conduct the endotoxin method qualification using two additional batches of the bulk drug substance.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: December 31, 2021

3. To conduct the bioburden test with a 10 mL sample volume. The revised bioburden method should be qualified using three batches of in-process intermediates and bulk drug substance.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: December 31, 2021

4. Provide the shipping validation summary report for drug product distribution to the US, performed in the actual shipping lanes under worst-case conditions (summer).

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: August 31, 2018

5. To perform a leachable study to evaluate leachables from the manufacturing process and the container closure system in OXERVATE (cenegermin-bkbj) drug product. The analysis will be performed using one drug product lot analyzed at release. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: December 31, 2019

6. To perform real time shipping validation studies to support the stability of OXERVATE (cenegermin-bkbj) drug product vials shipped from the DP manufacturing site in Italy to the US. The shipping study should evaluate product quality before and after shipping using worst-case shipping conditions of distance, duration, temperature, mode of transportation and vibration. The study should be performed with drug product manufactured with a process representative of the commercial process, same formulation and packaged in the same container closure system as that proposed for commercial batches. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: October 31, 2019

7. To establish a two-tiered reference material system for OXERVATE, comprised of primary and secondary (working) reference materials prepared from lot(s) representative of production and clinical materials. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2019

8. To conduct structure-function studies to better understand whether all critical aspects of NGF biological function relevant to receptor binding are adequately controlled by the current TF-1 cell based assay, that only assesses NGF activity through binding the TrkA.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: September 30, 2019

9. To implement a control reference material for the potency assay to improve control over the assay variability and provide additional assurance that the RS is performing as expected during routine potency testing. The potency assay control material should perform within established acceptance criteria relative to the reference standard. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on August 16, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: December 31, 2019

Submit clinical protocols to your IND 115892 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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 Health Project Manager for this application.

If you have any questions, call Derek Alberding, Regulatory Health Project Manager, at (240) 402-0963.

Sincerely,

{See appended electronic signature page}

Peter Stein, M.D.
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES: Content of Labeling
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/

PETER P STEIN
08/22/2018