CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214383Orig1s000

Trade Name:	Pepaxto for injection
Generic or Proper Name:	melphalan flufenamide
Sponsor:	Oncopeptides AB
Approval Date:	February 26, 2021
Indication:	In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD-38 directed monoclonal antibody.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 214383

ACCELERATED APPROVAL

Oncopeptides AB
c/o Veristat, LLC
Attention: Mara Holinger, PhD, RAC
Vice President of Regulatory Affairs
134 Turnpike Road, Suite 200
Southborough, MA 01772

Dear Dr. Holinger:

Please refer to your new drug application (NDA) dated June 30, 2020, received June 30, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pepaxto (melphalan flufenamide) for injection.

This new drug application provides for the use of Pepaxto (melphalan flufenamide) in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD-38 directed monoclonal antibody.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 Food and Drug Administration (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, text for the Patient Package Insert).

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on December 4, 2020, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214383**." 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 Pepaxto (melphalan flufenamide) for injection shall be 18 months from the date of manufacture when stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F) and protected from light.

ADVISORY COMMITTEE

Your application for Pepaxto was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated February 24, 2021. This requirement, along with required completion dates, is listed below.

[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.

4030-1 Submit the final study report and datasets from a randomized phase 3 clinical trial that verifies and describes the clinical benefit of melphalan flufenamide in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive melphalan flufenamide compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival assessed by an Independent Review Committee. The secondary endpoints should include overall response rate and overall survival.

Final Protocol Submission:	03/2021
Trial Completion:	08/2021
Final Report Submission:	02/2022

Submit clinical protocols to your IND 116362 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. 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.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse reactions and the safety in patients with different body sizes receiving a fixed dose of melphalan flufenamide; elevated drug levels in the presence of renal impairment and QT prolongation in patients receiving melphalan flufenamide.

In addition, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of increased risk of serious adverse events including hematologic toxicities in U.S. racial and ethnic minority patients with relapsed or refractory multiple myeloma.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify these unexpected serious risks and assess the signal of increased risk of serious adverse events in U.S. racial and ethnic minority patients with relapsed or refractory multiple myeloma.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4030-2 Submit an integrated analysis from clinical trials evaluating the fixed dose of melphalan flufenamide in patients with relapsed or refractory multiple myeloma with low body weight, to characterize and determine the exposure and rate of serious adverse reactions including grade ≥ 3 thrombocytopenia and neutropenia in patients with varying body sizes. Include a characterization of all serious adverse events, and the exposure-response relationship for efficacy and safety in the final report.

The timetable you submitted on February 24, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	05/2021
Final Analysis Plan Submission:	06/2021
Trial Completion:	08/2021
Final Report Submission:	02/2022

4030-3 Submit an integrated final report containing data from clinical trials including trial OP-108 to further characterize the exposure of melphalan flufenamide, the increased risk of serious adverse events including hematologic toxicities, and efficacy among U.S. racial and ethnic minorities including Black patients with relapsed or refractory multiple myeloma. Provide the pharmacokinetic analysis in the interim report.

The timetable you submitted on February 24, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	04/2022
Final Analysis Plan Submission:	10/2022
Interim Report Submission:	04/2023
Trial Completion:	06/2024
Final Report Submission:	12/2024

4030-4 Conduct a clinical pharmacokinetic study to determine a safe and appropriate dose of melphalan flufenamide in patients with CLcr < 45 mL/min. The number of patients recruited into groups of CLcr 30 to 44 mL/min and CLcr <30 mL/min should be sufficient to adequately characterize PK and safety profiles in each subgroup. Design and conduct the study in accordance with the draft FDA Guidance for Industry titled, *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling.*

The timetable you submitted on February 24, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2021
Study Completion:	09/2022
Final Report Submission:	02/2023

4030-5 Conduct a clinical study to characterize the risk of QTc prolongation (i.e., exclude large mean increases of >20 msec in the QTc interval) with melphalan flufenamide and its active metabolite, melphalan. Design and conduct the study in accordance with the ICH E14 Guidances for Industry titled, *E14 Clinical Evaluation of QT/QTc* and *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3) Guidance for Industry*.

The timetable you submitted on February 24, 2021, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2021
Final Protocol Submission:	12/2021
Trial Completion:	05/2023
Final Report Submission:	10/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 116362 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[4]

REPORTING REQUIREMENTS

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

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 Project Manager for this application.

If you have any questions, call Bernetta Lane, Regulatory Health Project Manager, at (301) 796-0937.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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

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/

MARC R THEORET
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