

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212306Orig1s000

Trade Name: XPOVIO™

Generic or Proper Name: selinexor

Sponsor: Karyopharm Therapeutics, Inc.

Approval Date: July 03, 2019

Indication: In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

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APPROVAL LETTER



NDA 212306

ACCELERATED APPROVAL

Karyopharm Therapeutics, Inc.
Attention: Tanya Lewis
Senior Vice President, Regulatory Affairs
85 Wells Avenue
Newton, MA 02459

Dear Ms. Lewis:

Please refer to your new drug application (NDA) dated August 5, 2018, received August 6, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XPOVIO™ (selinexor) tablets, 20 mg.

We acknowledge receipt of your major amendment dated March 13, 2019, which extended the goal date by three months.

This new drug application provides for the use of XPOVIO (selinexor) tablets in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

APPROVAL & LABELING

We have completed our review of this application, as amended. 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, Medication Guide). 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

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>.

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 June 17 & 28, 2019, 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 212306.**” Approval of this submission by FDA is not required before the labeling is used.

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 trials 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 June 17, 2019. This requirement, along with required completion dates, is listed below.

- | | |
|--------|--|
| 3657-1 | Complete and submit a final report with full datasets from the ongoing multicenter, randomized, controlled, phase 3 clinical trial (KCP-330-023) comparing selinexor in combination with bortezomib and dexamethasone (SVd) to bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. The primary objective is to compare progression free survival (PFS) in both treatment arms. |
| | Trial Completion: 03/2020
Final Report Submission: 09/2020 |
| 3657-2 | Conduct a randomized phase 2 clinical trial of selinexor in combination with dexamethasone to characterize the safety and efficacy of at least two different doses of selinexor, which are lower than the dosing regimen of 80 mg on Days 1 and 3 of each week, in patients with relapsed refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least two proteasome inhibitors, at |

least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. The primary objective is to assess the overall response rate in all treatment arms according to International Myeloma Working Group (IMWG) criteria by investigator assessment. The trial should include one interim analysis for futility. The results of this trial will be used to inform the optimal dose for selinexor in this patient population. Submit a final report with full datasets.

Preliminary Protocol Submission:	08/2019
Final Protocol Submission:	10/2019
Interim Analysis:	12/2020
Trial Completion:	06/2021
Final Report Submission:	10/2021

3657-3 Conduct a hepatic impairment trial in patients with NCI classification of moderate, severe hepatic impairment or Child-Pugh classes B, and C compared to patients with normal hepatic function since drug clearance may be reduced with hepatic impairment.

Preliminary Protocol Submission:	08/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2021
Final Report Submission:	09/2021

3657-4 Conduct a drug interaction trial in patients to evaluate the effect of co-administration of a strong CYP3A4 inhibitor on the pharmacokinetics of selinexor.

Preliminary Protocol Submission:	08/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2021
Final Report Submission:	09/2021

Submit clinical protocols to your IND 114042 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3657-5 Conduct a dedicated drug interaction trial in patients to determine the effect of co-administration of a strong CYP3A4 inducer on the pharmacokinetics of selinexor.

The timetable you submitted on June 17, 2019, states that you will conduct this study according to the following schedule:

Preliminary Protocol Submission:	09/2019
Final Protocol Submission:	03/2021
Trial Completion:	03/2022
Final Report Submission:	09/2022

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 114042 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment 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. 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

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

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

REPORTING REQUIREMENTS

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

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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 FDA.gov.⁴

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 Thomas Iype, Regulatory Health Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Acting Deputy Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - o Prescribing Information
 - o Medication Guide

⁴ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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
07/03/2019 11:52:32 AM