NDA 212306

NDA ACCELERATED APPROVAL
RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

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

Dear Ms. Lewis:[1]

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 also refer to our approval letter dated July 3, 2019 which contained the following errors:

- Post marketing requirement (PMR) 3657-2, required to assess a signal of a serious risk of adverse events along with efficacy in lower doses of selinexor was not correctly defined and inadvertently listed under the Accelerated Approval Regulations title 21 of the Code of Federal Regulations (CFR) 314.510.

- In addition, PMRs 3657-3 and 3657-4, required under Section 505(o)(3) of the FDCA were also inadvertently listed under the Accelerated Approval Regulations 21 CFR 314.510.

This replacement approval letter incorporates the release of PMR 3657-2 and replaces this PMR with the revised PMR 3657-6 to clearly communicate the purpose of this requirement and also correctly requires PMRs 3657-6, 3657-3 and 3657-4 under Section 505(o)(3) of the FDCA. The effective approval date will remain July 3, 2019, the date of the original approval letter.

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

[1] 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.

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 Food and Drug Administration (FDA) automated drug registration and listing system (eLIST), as described at FDA.gov.[2] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) 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.*[3]

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, 2019 and June 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 *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 212306**." Approval of this submission by FDA is not required before the labeling is used.

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[3] 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.

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

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.

RELEASE FROM POSTMARKETING REQUIREMENT

We refer to postmarketing requirement 3657-2 cited in our July 3, 2019, accelerated approval letter and listed below.

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.

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

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

We have determined that you are released from the above postmarketing requirement for the following reason:

> PMR 3657-2 does not clearly communicate the purpose to assess a signal of a serious risk of adverse events in lower doses of selinexor under Section 505(o)(3) of the FDCA.

The above postmarketing requirement will be replaced by the new postmarketing requirement 3657-6 as described below:

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 assess a signal

of serious risk of adverse events including myelosuppression, gastrointestinal toxicity, infection, hyponatremia, and neurological toxicity in patients receiving lower or alternative dosage regimens of selinexor in combination with dexamethasone.

Additionally, 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of elevated drug levels in the presence of moderate or severe hepatic impairment, and to determine appropriate dose adjustment when selinexor is used concomitantly with strong CYP3A inhibitors.

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 assess a signal of serious risk of adverse events including myelosuppression, gastrointestinal toxicity, infection, hyponatremia, and neurological toxicity in patients receiving lower or alternative dosage regimens of selinexor in combination with dexamethasone and to identify unexpected serious risks of elevated drug levels in the presence of moderate or severe hepatic impairment, and to determine appropriate dose adjustment when selinexor is used concomitantly with strong CYP3A inhibitors.

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

3657-6 Conduct a randomized, phase 2 clinical trial evaluating at least two lower doses or alternative dosage regimens of selinexor in combination with dexamethasone in patients with multiple myeloma to characterize and determine the rate of serious adverse reactions including myelosuppression, gastrointestinal toxicity, infection, hyponatremia, and neurological toxicity in all treatment arms. Patients in this trial should have relapsed refractory multiple myeloma, have received at least four prior lines of therapy, and have disease that is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. Include a characterization of all serious adverse events, dose-reductions, interruptions, and discontinuations due to serious adverse events, and efficacy in all treatment arms in the final report. Efficacy should be assessed by overall response rate according to

International Myeloma Working Group (IMWG) criteria by investigator assessment.

The timetable you submitted on December 7, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	02/2020 (completed)
Interim Analysis:	03/2021
Trial Completion:	09/2021
Final Report Submission:	01/2022

Submit datasets with the final report.

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.

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

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 coadministration of a strong CYP3A4 inhibitor on the pharmacokinetics of selinexor.

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

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

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.[4]

[4] 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.

Submit clinical protocols to your IND 114042 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.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

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 314.55, 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 314.55, 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, Medication Guide, and 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, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

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

REPORTING REQUIREMENTS

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

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.

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
  - Prescribing Information
  - Medication Guide

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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