DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202714

**ACCELERATED APPROVAL**

Onyx Pharmaceuticals, Inc.
Attention: Sunita Zalani, Ph.D.
Vice President, Global Regulatory Affairs
249 East Grand Avenue
South San Francisco, CA 94080

Dear Dr. Zalani:

Please refer to your New Drug Application (NDA) dated September 26, 2011, received September 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kyprolis™ (carfilzomib) for Injection, 60 mg.

We acknowledge receipt of your amendments dated November 17 and 18, 2011; December 9, 12, 13, 16, 19 and 20, 2011; January 5, 20, 27 and 30 (2), 2012; February 9, 15 (2) and 29, 2012; March 2 and 9, 2012; April 9, 16 and 27, 2012; May 1, 14, 22 (2) and 23, 2012; June 13 and 28, 2012; and July 3, 9, 12, 16 and 17 (2), 2012.

This new drug application provides for the use of Kyprolis™ (carfilzomib) for Injection for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

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 text. 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 FDA automated drug registration and listing system (eLIST), 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). 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.

## CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202714**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Karen Bengtson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2189
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Karen Bengtson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2189
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

## ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such trials with due diligence. If postmarketing trials fail to verify that clinical benefit is conferred by carfilzomib, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530(b), withdraw or modify approval. We remind you of your postmarketing requirement specified in your submission dated July 17, 2012.

This requirement, along with required completion dates, is listed below.

PMR 1908-1 Conduct a randomized controlled trial per Protocol PX-171-009, as finalized, to compare carfilzomib-lenalidomide dexamethasone with lenalidomide dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety. Patients' disease is required to show evidence of progression after prior therapy. The trial includes 792 patients. The randomization will balance known important prognostic factors. The goal of the trial is to evaluate the primary endpoint of progression-free survival (PFS) for the carfilzomib-containing arm, as determined by an independent review committee blinded to the treatment given.

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| Final Protocol Submission: | January 2010 |
| Trial Completion: | December 2013 |
| Final Report Submission: | June 2014 |

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, 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, you are exempt from this requirement.

**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 signals of the serious risks of cardiac, pulmonary, infusion-related, hepatic, and renal toxicities, and toxicities of new treatment regimens of Kyprolis™ (carfilzomib) for Injection.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the serious risks of cardiac, pulmonary, infusion-related, hepatic, and renal toxicities, and toxicities of new treatment regimens of Kyprolis™ (carfilzomib) for Injection.

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

PMR 1908-2 Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. You have agreed to conduct this trial as a cardiac sub-trial within your ongoing Protocol 2011-003 (ENDEAVOR). The primary objective is to compare changes in cardiac function between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial.

The main trial protocol (2011-003) must require a baseline resting ECG and transthoracic ECHO to assess left ventricular (LV) function on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. For the cardiac sub-trial, a subset of patients from the main trial will be assessed for LV and right ventricular (RV) function with transthoracic ECHO (or MUGA for those sites using MUGA at baseline) periodically throughout trial treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. This cardiac sub-trial must include a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes must be pre-specified and outlined in the SAP for this cardiac toxicity trial. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the protocol treatment given.

In addition, any patient in the main trial who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an ECHO performed to assess LV and RV function as part of the evaluation of that AE.

Submit a complete cardiac sub-trial protocol for review and concurrence before commencing the sub-trial.

The timetable you submitted on July 17, 2012, states that you will conduct this sub-trial according to the following schedule:

2011-003 (ENDEAVOR) Phase 3 Cardiac Sub-Trial

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| Final sub-trial Protocol Submission: | January 2013 |
| Trial Completion: | November 2015 |
| Final Report Submission: | May 2016 |

PMR 1908-3 Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the pulmonary toxicities associated with carfilzomib. The primary objective is to compare pulmonary toxicities between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial. You have agreed to conduct this pulmonary sub-trial within your ongoing Protocol 2011-003. On all patients enrolled in the main trial, 2011-003, during screening, obtain a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess right ventricular size, thickness, and function, and to serve as the baseline ECHO for later comparisons on all patients. In the pulmonary sub-trial, among a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm), assess this sub-group periodically for pulmonary artery pressures and right ventricular function with repeat transthoracic ECHO throughout trial treatment and at the time of End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. Emergent pulmonary toxicities must be further characterized in all patients receiving carfilzomib in the main trial also, to include at least the following: time course of onset and resolution, oximetry and/or blood gases, and consultation with a pulmonary specialist, when clinically appropriate, to provide further documentation of the nature of the emergent condition. Document the response to oxygen supplementation and other treatment measures. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the treatment given.

In the pulmonary sub-trial protocol, pre-specify how comparisons will be performed for changes between the two groups for outcomes related to pulmonary hypertension, right ventricular function, and clinical pulmonary safety events. Additionally, for all patients enrolled in the main trial, any patient who has a cardiac or pulmonary AE that is considered a clinically significant AE must have a follow-up ECHO at the time of the event to assess LV, RV, and pulmonary artery function.

Submit a complete pulmonary sub-trial protocol for review and concurrence before commencing the sub-trial.

The timetable you submitted on July 17, 2012, states that you will conduct this trial according to the following schedule:

2011-003 (ENDEAVOR) Phase 3 Pulmonary Sub-Trial

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| Final sub-trial Protocol Submission: | January 2013 |
| Trial Completion: | November 2015 |
| Final Report Submission: | May 2016 |

PMR 1908-4 Conduct a clinical trial (2011-003 ENDEAVOR) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m$^2$ in patients with multiple myeloma.

The timetable you submitted on July 17, 2012, states that you will conduct this trial according to the following schedule:

2011-003 (ENDEAVOR) Phase 3 Trial

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| Final Protocol Submission: | March 2012 |
| Trial Completion: | November 2015 |
| Final Report Submission: | May 2016 |

PMR 1908-5 Conduct a clinical trial (PX-171-007) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m$^2$ in patients with multiple myeloma

The timetable you submitted on July 17, 2012, states that you will conduct this trial according to the following schedule:

PX-171-007 Phase 2 Trial

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| Final Protocol Submission: | August 2007 |
| Trial Completion: | June 2014 |
| Final Report Submission: | December 2014 |

PMR 1908-6 Conduct a clinical trial in patients with hepatic impairment to assess safety and PK characteristics of carfilzomib administered as a 30 minute infusion. The number of patients enrolled in the trial should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the labeling. The duration of the trial should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimized to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

The timetable you submitted on July 17, 2012, states that you will conduct this trial according to the following schedule:

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|---|---|
| Final Protocol Submission: | March 2013 |
| Trial Completion: | December 2015 |
| Final Report Submission: | May 2016 |

PMR 1908-7 Conduct one or more clinical trials including Phase 3 Protocol 2011-003, supplemented as needed by an additional trial, to evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment and those on chronic dialysis following the administration of carfilzomib when given as a 30 minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment who receive carfilzomib doses of 20/56 mg/m$^2$ using the 30 minute infusion as planned in your upcoming Phase 3 trial Protocol 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m$^2$ or highest clinical dose in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

The timetable you submitted on July 17, 2012, states that you will conduct this trial according to the following schedule:

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|---|---|
| Final Protocol Submission: | March 2013 |
| Trial Completion: | December 2015 |
| Final Report Submission: | May 2016 |

Submit the protocols to your IND 071057, with a cross-reference letter to this NDA. Submit 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 references, and approved package insert (PI)/Medication Guide/patient PI (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

## 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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

## POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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 Karen Bengtson, Regulatory Project Manager, at (301) 796-3338.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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RICHARD PAZDUR
07/20/2012