DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202714/S-010

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Onyx Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen Inc.
Attention: Brian Stouch, RAC
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-1-A
Thousand Oaks, CA 91320-1799

Dear Mr. Stouch:

Please refer to your Supplemental New Drug Application (sNDA) dated July 22, 2015, received July 22, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kyprolis® (carfilzomib) for injection, 60 mg.

This "Prior Approval" supplemental new drug application provides for modifications to the indications for Kyprolis® (carfilzomib) based upon confirmatory Study 2011-003 (ENDEAVOR), entitled "*A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone (Kd) vs. Bortezomib Plus Dexamethasone (Vd) in Patients with Relapsed Multiple Myeloma*".

Kyprolis® (carfilzomib) is approved for the following indications:

1. In combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy

2. As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy

This supplement gives regular approval to the Kyprolis® (carfilzomib) monotherapy indication and provides for the fulfillment of postmarketing requirements (PMRs) 1908-2, 1908-3, and 1908-4.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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 titled "*SPL Standard for Content of Labeling Technical Qs and As*" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART H FULFILLED

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your requirements made under 21 CFR 314.510.

We also note that the following Accelerated Approval PMR was previously fulfilled on July 24, 2015.

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.

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

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.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submission dated July 22, 2015, containing the final reports for the following postmarketing requirements listed in the July 20, 2012 approval letter.

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

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

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

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

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the July 20, 2012 approval letter that are still open.

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.

Since Kyprolis® (carfilzomib) was approved on July 20, 2012, we have become aware of analyses suggesting an increased risk of cardiac and pulmonary toxicity with the 20/56 mg/m^2 dose of carfilzomib used in clinical trials and the potential for unexpected serious risks associated with long-term therapy in these patients. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.
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 the risk of serious cardiac and pulmonary toxicity and other unexpected serious risks associated with long-term use of the 20/56 mg/m^2 dose of carfilzomib.

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 a serious risk of increased cardiac and pulmonary toxicity and other unexpected serious risks associated with the long-term use of the 20/56 mg/m^2 dose of carfilzomib.

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

PMR 3022-1

Characterize safety of long-term use in patients treated with Kyprolis (carfilzomib) 20/56 mg/m^2 plus dexamethasone. Submit a final report and datasets with safety and efficacy outcomes of current clinical trial 2011-003 (ENDEAVOR) with at least 3 years of follow-up data.

The timetable you submitted on January 20, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2016
Trial Completion:	06/2017
Final Report Submission:	12/2017

Submit the protocol to your IND 071057, with a cross-reference letter to this NDA. Submit all final report(s) 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3022-2 Characterize the comparative safety and efficacy of the 20/27 mg/m^2 and the 20/56 mg/m^2 regimens of carfilzomib. Submit a study report with safety and efficacy outcomes of SWOG Protocol S1304 and your analysis of what clinical parameters might affect the choice of carfilzomib regimen for a particular patient.

The timetable you submitted on January 20, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2016
Study Completion:	07/2017
Final Report Submission:	01/2019

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

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

If you have any questions, call Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ANN T FARRELL
01/21/2016