

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202714Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	June 18, 2012
<b>From</b>	Albert Deisseroth, MD, PhD
<b>Subject</b>	Cross-Discipline Team Leader (CDTL) Review
<b>NDA/BLA #</b>	NDA 202714
<b>Supplement#</b>	
<b>Applicant</b>	Onyx Pharmaceuticals
<b>Date of Submission</b>	
<b>PDUFA Goal Date</b>	July 27, 2012
<b>Name / Established (USAN) names</b>	Carfilzomib (Kyprolis)
<b>Dosage forms / Strength</b>	Lyophilized powder (60 mg/vial) in 29 ml sterile water (2 mg/ml) for intravenous administration
<b>Applicant's Proposed Indication(s)</b>	Treatment of patients with relapsed and refractory multiple myelomas who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent
<b>Recommended:</b>	Accelerated Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Thomas Herndon, MD
Statistical Review	Kallappa M. Koti, PhD
Pharmacology Toxicology Review	Todd Palmby, PhD and Haleh Saber, PhD
ONDQA-CMC Reviews	Josephine Jee, PhD, William Adams, PhD and Janice Brown, PhD
Biopharmaceutics Review	Honda Mahayni, PhD and Angelica Dorantes, PhD
Microbiology Review	John Metcalfe PhD, and Bryan Riley, PhD
Clinical Pharmacology Review	Bahru Habtemariam, PharmD and Julie Bullock, PharmD
OSI/DG CPC Review	Anthony Orenca, MD

## 1. Introduction

On January 28, 2011 and on November 26, 2011, Onyx Pharmaceuticals submitted components of a New Drug Application (NDA) for carfilzomib for the treatment of patients with relapsed or refractory multiple myeloma. This application is based upon the results of Study PX-171-003 Part 2 (Study 3), a Phase 2 single-arm trial that enrolled 266 patients with refractory or relapsed multiple myeloma who had received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent (IMiD) for the study of the efficacy of carfilzomib. The primary endpoint was overall response rate (ORR) as adjudicated by an independent review committee (IRC). The results of a total of four Phase 2 single arm studies of carfilzomib treatment of 526 patients with relapsed multiple myeloma were used to assess the safety of carfilzomib.

### **Efficacy as Measured by the Primary Endpoint**

The ORR to carfilzomib in patients with relapsed multiple myeloma entered onto PX-171-003 (N=266 patients) was 22.9%, whether analyzed by the Applicant or by the FDA.

### **Safety**

The safety data suggests that there is a low percentage of patients with relapsed multiple myeloma who develop life-threatening cardiac adverse events due to carfilzomib. Cardiac toxicity was prominent among “On Study Deaths”, serious adverse events, and adverse events contributing to discontinuation of carfilzomib. In addition to the cardiac adverse events, there were significant pulmonary, and to a lesser extent hepatic adverse events. All of these were observed at a low frequency, however. There were also reactions and adverse events associated with carfilzomib infusion that need further characterization. As these safety signals were identified using data from a single arm study, it is not possible to distinguish whether these adverse events arose from carfilzomib, pre-treatment features associated with the patient population, or the prior treatment history of these patients.

### **Benefit Risk Assessment:**

Since carfilzomib produced an ORR of 22.9% in the primary efficacy study in a population of patients 89% of whom were resistant to bortezomib, and since the Safety Analysis of 526 patients with multiple myeloma entered onto phase 2 trials showed only a low frequency of life-threatening adverse events involving the heart, lung and liver, the benefit-risk is favorable.

**CDTL Recommendation:** The recommendation of the CDTL reviewer is accelerated approval (Subpart H) with the PMRs outlined below.

### **PMR 1: Requirement under Subpart H to Verify Clinical Benefit**

To verify and describe the clinical benefit of carfilzomib. In addition to PX-171-009, the Applicant will conduct one or more randomized controlled trials, such as Protocol 2011-003, which as finalized compares carfilzomib-dexamethasone with bortezomib-dexamethasone in a population of patients with multiple myeloma whose disease has relapsed after previous response to at least one but not more than three prior therapies, to further assess the efficacy and safety of carfilzomib. Eligible patients are required to show evidence of progression after prior therapy. Estimated sample size is 700. The randomization will balance known important prognostic factors. The carfilzomib will be administered as a 30 minute infusion at a dose of 20/56 mg/m<sup>2</sup> twice a week X3 every 28 days. The goal of the trial is to demonstrate superiority of carfilzomib-dexamethasone as compared to bortezomib-dexamethasone, using the primary endpoint of progression-free survival (PFS) as determined by an IRC blinded to the treatment given.

## **PMR 2: Cardiac Safety Trial**

Cardiac dysfunction is common in heavily pretreated patients with multiple myeloma. Cardiac dysfunction has been observed with carfilzomib administration, and the safety of carfilzomib in the relapsed myeloma population is not well characterized.

Therefore, the Applicant will conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. This trial can be a sub-study within Protocol 2011-003, or it may be a separate trial with this safety objective. 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.

If the Applicant chooses to add this sub-trial to Protocol 2011-003, Protocol 2011-003 must require a resting ECG and a baseline transthoracic ECHO to assess left ventricular ejection fraction (LVEF) on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. A subset of patients from both trial treatment arms should be assessed for LVEF and right ventricular (RV) function with transthoracic ECHO periodically throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. The subset of patients 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 in the subset of patients must be pre-specified and outlined in the SAP for this sub-study. Readers of the ECHOs must be blinded to the treatment arm.

In addition, any patient who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an additional ECHO performed to assess left ventricular (LV) and right ventricular (RV) function as part of the evaluation of that AE; this applies to all patients enrolled in the study.

The Applicant must submit a complete protocol to the FDA for review and concurrence before commencing the trial.

### **PMR 3: Pulmonary Safety Trial**

Pulmonary toxicities have been observed with carfilzomib, but they are not well characterized.

Therefore, the Applicant will 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. This could be done within the proposed Protocol 2011-003 as a sub-study or as a separate study. If performed as a sub-study of protocol 2011-003, the Applicant must obtain a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess RV size, thickness, and function. Subsequently, a subset of patients from both treatment arms should be assessed periodically for pulmonary artery pressures and RV function with repeat transthoracic ECHO throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. Emergent pulmonary adverse events must be further characterized in all patients receiving carfilzomib, to include a repeat ECHO to evaluate RV function and pulmonary artery pressures, the time course of onset and resolution, oximetry and/or blood gases, and consultation with a pulmonary specialist, when available, to provide further documentation of the nature of the emergent condition. The Applicant must document the response to oxygen supplementation and other treatment measures.

A minimum of 100 patients and a maximum of 300 patients total are necessary (50 to 150 patients per treatment arm). The Applicant must pre-specify how comparisons will be performed for changes between the two groups for outcomes related to pulmonary hypertension, RV function, and clinical pulmonary safety events. Additionally, 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. This evaluation is for all patients enrolled in the study.

### **PMR 4: Study of Carfilzomib Administered as a 30-Minute Infusion**

The proposed dose of carfilzomib submitted as part of NDA 202714 is the 20 mg/m<sup>2</sup> during Cycle 1 and 27 mg/m<sup>2</sup> during Cycle 2 (known as the 20/27 regimen), administered intravenously as a bolus over 2 to 10 min. The Applicant has completed a randomized study which isolates the effect of carfilzomib using the 20/27 regimen. The Applicant will conduct a safety study using the 30 minute intravenous infusion of carfilzomib at the dose of the 20 mg/m<sup>2</sup> during Cycle 1 and 56 mg/m<sup>2</sup> during Cycle 2 (known as the 20/56 regimen) in patients with multiple myeloma.

The Applicant will conduct the safety evaluation using either of the following two options or propose an alternative option for Agency review and concurrence:

- Conduct the study as part of the planned Phase 3 trial (Protocol number 2011-003),

OR

- Conduct a stand-alone safety study in patients receiving carfilzomib. This study must be conducted for sufficient duration in order to detect and assess safety signals. If the Applicant chooses to do a stand safety trial, a complete study protocol should be submitted to the Agency for review and concurrence.

### **PMR 5: Hepatic Impairment Study**

The Applicant will conduct a clinical trial in patients with hepatic impairment to assess safety and PK characteristics of carfilzomib. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant a dosage adjustment of the recommendations in the labeling. The duration of the study should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol. The Applicant must submit the protocol for Agency review and concurrence prior to initiation.

### **PMR 6: Renal Impairment Study**

Since PK assessment in the renal impairment study was conducted following carfilzomib doses of 15 and 20 mg/m<sup>2</sup> given intravenously over 2 – 10 minutes, and since this dosing regimen may not necessarily produce clinical responses at the level that would be seen with higher doses, the Applicant must evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment 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 that receive carfilzomib doses using the 20/56 mg/m<sup>2</sup> regimen and the 30 minute infusion as planned in the upcoming Phase 3 trial Protocol number 2011-003. The Applicant should collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. The Applicant should conduct this renal impairment evaluation using either of the following two options or propose an alternative option for Agency review and concurrence.

## **2. Background**

### **Carfilzomib**

Carfilzomib is a second-generation proteasome inhibitor. Carfilzomib consists of an epoxyketone pharmacophore attached to a tetrapeptide backbone. The epoxyketone pharmacophore of carfilzomib forms an irreversible, covalent bond functioning as an inhibitor of the chymotrypsin-like activity of the 20S proteasome, the proteolytic core particle within the 26S proteasome complex, when carfilzomib is given in a dose range of 20 to 27 mg/m<sup>2</sup>. Following the irreversible binding of carfilzomib to the 20S proteasome, proteasome activity is restored through cellular synthesis of new proteasome proteins.

### **Clinical**

#### **Multiple Myeloma**

Multiple myeloma is a malignancy of plasma cells. These cells accumulate in the bone marrow resulting in destruction of boney structures and marrow failure. Symptoms and signs of the disease include bone pain and bone damage, hypercalcemia, renal failure, and anemia. Affected individuals may also have frequent infections, weight loss, and weakness or numbness. Loss of function of visceral organs due to deposition of light chains and infiltration by neoplastic plasma cells can occur as well. Multiple myeloma is a disease primarily of older individuals.

#### FDA Approved Agents for Multiple Myeloma

There are 7 drugs that are currently approved for the treatment of multiple myeloma in multiple drug classes (Table 1). Six of these drugs have received full approval, while one of these drugs (thalidomide) was approved under the accelerated approval pathway and has not received full approval for multiple myeloma. Both thalidomide and lenalidomide are approved under Subpart H since they are under restricted distribution programs. Dexamethasone is approved for the treatment of hematologic malignancies. All of these agents would be considered to be available therapy under the regulations.

**Table 1. FDA Approved Drugs for Multiple Myeloma**

Class	Drug	FDA Approval
Alkylating agents	Melphalan	Regular
	Cyclophosphamide	Regular
Anthracyclines	Liposomal doxorubicin (Doxil™)	Regular
Nitrosureas	Carmustine	Regular
ImiDs	Thalidomide	Accelerated*
	Lenalidomide	Regular*
Proteasome Inhibitors	Bortezomib	Regular

\*Approved with restricted distribution under Sub-part H

The current treatment for multiple myeloma focuses on therapies that decrease the clonal plasma cell population resulting in an improvement in the signs and symptoms of the disease. The treatment chosen for patients with multiple myeloma depends on the age and performance status of the patient, as well as on the stage of the disease. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation has become a standard treatment for patients under the age of 65 years. Conventional dose combination chemotherapy is given as initial therapy prior to the use of myeloablative therapy/autologous stem cell transplant. Common conventional dose induction chemotherapy regimens include: bortezomib-based chemotherapy regimens, thalidomide/dexamethasone-based chemotherapy regimens, and lenalidomide/dexamethasone-based chemotherapy regimens. Autologous stem cell transplantation is the most common type of stem cell transplantation used to treat patients with multiple myeloma. None of the above cited treatments are curative. Allogeneic stem cell transplantation is the only therapy for multiple myeloma that has the potential for a cure, but only a minority of patients is eligible for this treatment.

For patients over the age of 65 years with multiple myeloma and patients with significant pre-treatment organ co-morbidities which would preclude the administration of any of the regimens described in the previous paragraph, treatment might include melphalan and prednisone with or without a proteasome inhibitor or an IMiD.

### Recurrent Disease

In patients with multiple myeloma who have relapsed following initial therapy, the choice of subsequent treatment depends on patient specific features, disease specific features, the duration of the response to the initial therapy, and the type of therapy used in the beginning. There are no established care pathways for patients with multiple myeloma who have relapsed following initial response or who are primary refractory.

Treatment approaches for patients who have been shown to progress following a response to initial therapy include retreatment with the drugs used for the initial therapy, as well as treatment with a different conventional dose chemotherapy regimen consisting of other available agents. These agents may include bortezomib, lenalidomide, thalidomide, anthracyclines, cyclophosphamide, and melphalan. Treatment of patients with multiple myeloma who have relapsed or are primary refractory can also include a second stem cell transplant if that treatment has already been delivered and the response was significant. A final option is therapy conducted under research protocols.

### **Regulatory**

#### Applicant's Proposed Indication

The Applicant's proposed indication is for the treatment of patients with relapsed and refractory multiple myelomas who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent. The Applicant has requested the approval of this indication on the basis of a single arm Phase 2 trial through the accelerated approval pathway.

#### Accelerated Approval

Accelerated approval is a regulatory pathway that applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments [e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy (CFR 314.500)].

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (CFR 314.510)).

Approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome (CFR 314.510).

### 3. CMC

Carfilzomib for Injection is formulated as a sterile white to off-white lyophilized cake or powder intended for reconstitution with Water for Injection (29 mL) and subsequent intravenous injection. The commercial marketing configuration is a (b) (4) vial containing 60 mg of carfilzomib. All excipients are commonly used in injectable dosage forms. The drug product is administered intravenously using the 20/27 mg/m<sup>2</sup> regimen (20 mg/m<sup>2</sup> in Cycle 1, escalating to 27 mg/m<sup>2</sup> in Cycle 2 and thereafter) over two (2) to ten (10) minutes, twice weekly on consecutive days for 3 weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle. The proposed indication is for the treatment of patients with relapsed and refractory multiple myeloma who has received at least two prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent. All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance was issued on 24-MAY-2012. (Note: This section was excerpted directly from the ONDQA Division Director's review memorandum).

**Recommendation of ONDQA:** The Applicant proposed an 18 month expiry for this product when stored in the commercial packaging at 5°C ± 3°C. Based on the stability data provided and in accordance with ICH Q1E, the Agency grants the proposed expiry. There is no need for additional confirmatory language in the action letter as there is no disagreement between the Applicant's proposed expiration dating period and that granted by the Agency. All CMC review issues have been resolved, and ONDQA recommends approval of this NDA. (Note: This section was excerpted directly from the ONDQA Division Director's review memorandum).

### 4. Nonclinical Pharmacology/Toxicology

Non-clinical pharmacology and toxicology studies to support carfilzomib (NDA 202714) for the treatment of relapsed and refractory multiple myeloma were reviewed by Jeffrey Bray, Ph.D. and Jessica J. Hawes, Ph.D. Studies conducted with intravenously administered carfilzomib included pharmacology, toxicokinetics and ADME, safety pharmacology, single- and repeat-dose toxicology (rat and monkey), and genetic toxicology (in vivo and in vitro). Reproductive and developmental toxicology studies were conducted in rats and rabbits to assess the effects of carfilzomib on embryo-fetal development. The studies cited in the review consist primarily of original research studies conducted by the Applicant.

Pharmacology studies submitted to the NDA support that carfilzomib is a proteasome inhibitor that irreversibly binds to the active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. The mechanism of action of carfilzomib is the same as bortezomib (i.e., inhibition of the 20S proteasome), although differences exist in their abilities to inhibit the chemotropism-like, peptidyl-glutamyl peptide-hydrolyzing (PGPH)-like and trypsin like activities of the 20S proteasome and in that bortezomib binding to the 20S proteasome is reversible. These differences may account for the distinct toxicity and activity profile of carfilzomib. As carfilzomib is an irreversible proteasome inhibitor, recovery of proteasome inhibition requires production of new proteasome protein, which occurred in  $\geq 24$  hours, depending on the tissue. The Established Pharmacologic Class (EPC) determined to be most appropriate for carfilzomib is “proteasome inhibitor” since data provided in the NDA demonstrate that it has a similar mechanism of action as previously approved products in this class.

The clinical route of administration for carfilzomib is an intravenous infusion over 2 to 10 minutes. The majority of studies in animals submitted to this NDA (e.g., safety pharmacology, ADME, repeat-dose toxicology, in vivo genetic toxicology, reproductive and developmental toxicology) were conducted with bolus intravenous injections of carfilzomib. A series of studies in rats were conducted comparing the pharmacodynamics, pharmacokinetics and toxicities of Reference ID: 3141648 intravenous carfilzomib administered as a bolus injection, a 10-minute infusion or a 30-minute infusion. The C<sub>max</sub> and significant toxicities, including death and prerenal azotemia (elevated blood urea nitrogen and creatinine), observed following a bolus injection were reduced when administered as a 10- or 30-minute infusion, while a similar level of proteasome inhibition was maintained. These results suggest that some toxicities observed following administration of carfilzomib may be related to the C<sub>max</sub>. Adverse effects in rats and/or monkeys that were consistent with adverse events reported in clinical trials included cardiovascular (decreased blood pressure, increased heart rate, increased troponin-I, cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration), renal (glomerulonephropathy, tubular necrosis, dysfunction), gastrointestinal (necrosis/hemorrhage), pulmonary (hemorrhage/inflammation), hepatic (changes in serum transaminases) and hematopoietic (decreased platelets) toxicities.

Carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, but was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vivo mouse bone marrow micronucleus assay.

Carfilzomib caused embryo-fetal toxicity in rats and rabbits, but was not teratogenic. In rabbits, only a pilot, non-GLP embryo-fetal developmental toxicity study was conducted, which did not include a toxicokinetic analysis. In this study, carfilzomib caused embryo-fetal effects including increased pre- and postimplantation loss and early resorptions and a decrease in fetal weight as well as maternal toxicity. Therefore, this study was acceptable to confirm similar toxicities in a GLP embryo-fetal developmental toxicity study in rats, which included toxicokinetics. Section 8.1 Pregnancy in the package insert for carfilzomib reflects the lack of toxicokinetic data in rabbits with the comparison to

doses in patients based on body surface area rather than systemic exposure (AUC). The potential benefit of KYPROLIS in pregnant women in the indicated patient population may outweigh the potential risk to the developing fetus. Therefore, Pregnancy Category D is recommended. (Note: this section was excerpted directly from the review of the Nonclinical Pharmacology/Toxicology group).

**Recommendation of Nonclinical Pharmacology/Toxicology:** It is concluded that the pharmacology and toxicology data support the approval of NDA 202714 for carfilzomib. There are no outstanding nonclinical issues that would preclude the approval of carfilzomib for the proposed indication. (Note: this section was excerpted directly from the review of the Nonclinical Pharmacology/Toxicology group).

## 5. Clinical Pharmacology

Carfilzomib is a second generation proteasome inhibitor being developed for the treatment of patients with refractory and relapsed multiple myeloma. The proposed dosing regimen is 20 mg/m<sup>2</sup> during cycle 1 and 27 mg/m<sup>2</sup> for cycles 2 and beyond given as a 2-10 minute intravenous bolus infusion twice weekly on days 1, 2, 8, 9, 15 and 16 of a 28-day treatment cycle.

To support the proposed indication, the sponsor conducted a single arm trial in 266 patients using the proposed dosing regimen described above. The primary endpoint was overall response rate (ORR) which is a composite endpoint of complete response, very good partial response, and partial response. In this pivotal phase 2 trial, 22.9% of patients achieved the primary endpoint of ORR. One of the most important adverse events was liver enzyme elevation, with 6.4% of treated patients experiencing grade 3 or more ALT elevations. Exposure-response relationship was not evident for efficacy or safety.

Preclinical and clinical studies were conducted to characterize the disposition and drug-drug interaction potentials of carfilzomib. *In vitro* studies showed carfilzomib is metabolized in plasma by protein peptidase and epoxide hydrolysis. In total, these studies show the exposure to carfilzomib will not be influenced by other drugs and carfilzomib will not influence exposure to other drugs.

The ADME characteristics of carfilzomib were not conducted in humans; ADME data were available from a rat study. The rat ADME study showed 30.5% of the administered drug undergoes biliary elimination while about 26% of the administered drug is eliminated by the kidneys. A renal impairment study in cancer patients showed the C<sub>max</sub> and AUC of carfilzomib were similar across all renal function categories including patients with normal renal function and those with mild, moderate, and severe renal impairment, and those patients on chronic dialysis.

The proportion of the administered drug that undergoes biliary elimination has not been evaluated in humans. In addition, the occurrence of grade 3/4 ALT elevations in 6.4% of patients in the pivotal phase 2 study suggests those patients with pre-existing hepatic

impairment maybe at an increased risk of liver toxicity when treated with carfilzomib. In order to characterize the influence of hepatic function on the safety and pharmacokinetics of carfilzomib, a post marketing study in patients with hepatic impairment will be requested. (Note: this section was excerpted directly from the review of the Clinical Pharmacology group).

### **Recommendation of Clinical Pharmacology:**

**a. Recommendation:** This NDA is acceptable from a clinical pharmacology perspective provided that the applicant and the Agency come to an agreement regarding the labeling language and the identified clinical studies under the post marketing requirements (PMRs). (Note: this section was excerpted directly from the review of the Clinical Pharmacology group).

**b. Post Marketing Requirements** 1. Conduct a clinical trial in patients with hepatic impairment. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The duration of the study should be sufficient to reasonably characterize potential safety issues. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

Conduct the hepatic impairment trial according to the following schedule:

- i. Final Protocol Submission Date: 31 January 2013
- ii. Trial Completion Date: 30 September 2015
- iii. Final Report Submission: 31 March 2016

Since PK assessment in the renal impairment study was conducted following carfilzomib doses of 15/20 mg/m<sup>2</sup> given intravenously over 2 – 10 minutes and since this dosing regimen may not necessarily produce clinical responses at the level that would be seen with higher doses, evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment 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 that receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30 minute infusion as planned in your upcoming phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. Conduct your renal impairment evaluation using either of the following two options or propose an alternative option for our review and concurrence:

- i. Amend the planned Phase 3 trial (Protocol number 2011-003) to include patients with varying degrees of renal impairment and those on chronic dialysis. OR
- ii. Conduct a stand-alone renal impairment study in patients with varying degrees of renal impairment including patients with mild, moderate, severe renal function and those on chronic dialysis. Conduct the study for sufficient duration in order to detect and assess safety and efficacy signals. If you

choose to do a stand-alone renal impairment trial, submit a complete study protocol for review and concurrence by the Agency.

Final Protocol Submission Date: 31 January 2013.

Trial Completion Date: 30 September 2015

Final Report Submission: 31 March 2016

(Note: this section was excerpted directly from the review of the Clinical Pharmacology group).

## 6. Clinical Microbiology

The drug composition is shown in Table 2 below.

**Table 2: Drug Composition**

Ingredients	Function	Amount/Vial (Percent)	Amount/Vial (mg)
Carfilzomib	Active pharmaceutical ingredient		(b) (4)
Sulfobutylether beta-cyclodextrin	(b) (4)		
Anhydrous citric acid, USP, Ph. Eur.			
Sodium hydroxide, NF	pH adjustment		
(b) (4)	(b) (4)		

Abbreviations: NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopoeia;

(b) (4)

### A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The bulk drug solution is compounded in

(b) (4)

Note: This section was excerpted directly from the review of Microbiology).

### B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

**C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

**Recommendations of Microbiology:**

**A. Recommendation on Approvability** – NDA 202714/N-000 is recommended for approval on the basis of issues pertaining to product quality microbiology.

**B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

(Note: This section was excerpted directly from the review of Microbiology).

## **7. Clinical/Statistical- Efficacy**

The Applicant submitted study report includes results from 526 patients enrolled in 4 single arm studies that administered carfilzomib (CFZ) monotherapy in patients with relapsed and/or refractory multiple myeloma. Study PX-171-003, in patients with relapsed and refractory multiple myeloma, is presented in two study reports: Study Report PX-171-003 – Part 1 (A0), a completed pilot study, and Study Report PX-171-003 – Part 2 (A1), considered as the pivotal study. The pivotal study used a carfilzomib dose of 20 to 27 mg/m<sup>2</sup>. Study PX-171-004, in patients with relapsed or refractory multiple myeloma, is also reported in 2 study reports: on going Study Report PX-171-004 – Part 1 in bortezomib-treated patients and ongoing Study Report PX-171-004 – Part 2 in bortezomib-naïve patients. The primary endpoint was overall response rate (ORR) (≥ partial response [PR]) based on an Independent Review Committee (IRC) assessment.

The Applicant is undertaking a Phase 3 trial (PX-171-009). It is a 700-patient, multicenter, international, randomized, open-label study of lenalidomide with low dose dexamethasone (Rd) versus carfilzomib + Rd (CRd) with PFS as the primary endpoint in patients with relapsed or refractory MM after 1-3 prior therapies. This study will serve as the confirmatory trial.

The key efficacy findings based on all subjects (n=266) from study PX-171-003- Part 2 (A1) are:

- a. The overall response rate (ORR) among was 22.9% [95% CI: (18%, 28%)]. The ORR was significantly greater than 10% (p-value < 0.0001).
- b. Only one subject (0.4%) achieved complete response (CR).
- c. IRC assessed median duration of response (DoR) was 7.8 months [95% CI: (5.6, 9.2)].
- d. The clinical benefit rate (CBR) was 36% [95% CI: (30%, 41%)].
- e. IRC assessed median PFS was 3.7 months [95% CI: (2.8, 4.6)].
- f. One-hundred and thirty-two (50%) patients died during the study. The median overall survival was 15.4 months [95% CI: (12.4, 19.0)].

- g. A subset of subjects (not all subjects) was unresponsive or intolerant to all available agents. A summary of ORR and median DoR for subgroups of subjects who were unresponsive and intolerant to approved agents is provided in Table 4.2.1.

### **Statistical and Clinical Reviewers' Conclusions:**

The key efficacy findings based on all subjects from study PX-171-003- Part 2 (A1) are:

- a. The overall response rate (ORR) was 22.9% [95% CI: (18%, 28%)]. The ORR was significantly greater than 10% (p-value < 0.0001).
- b. IRC assessed median duration of response was 7.8 months [95% CI: (5.6, 9.2)].
- c. The clinical benefit rate (CBR) was 36% [95% CI: (30%, 41%)].
- d. One-hundred and thirty (50%) patients died during the study. The median overall survival was 15.4 months [95% CI: (12.4, 19.0)].
- e. IRC assessed median PFS was 3.7 months [95% CI: (2.8, 4.6)].
- f. A subset of subjects (not all subjects) were unresponsive or intolerant to all available agents.
- g. A summary of ORR and median DoR for subgroups of subjects who were unresponsive and intolerant to approved agents is provided in Table 4.2.1.

(Note: This section was excerpted directly from the review of the Statistical Review Division).

## **8. Safety**

### **Overview of the Safety Population**

The entire safety database consists of 768 patients who were exposed to at least one dose of carfilzomib. Some (156) of the 768 patients were patients with solid tumors or hematological diseases besides multiple myeloma (20%) while the majority (612) of patients had multiple myeloma (80%). The data included in the safety data base was from multiple Phase 1 (86 patients) and Phase 2 (526 patients) trials as shown below in Table 3. Of the 768 patients exposed to at least one dose of carfilzomib, there were 612 patients with relapsed refractory multiple myeloma. Among these 612 patients, 86 were enrolled in Phase 1 trials and 526 were enrolled in Phase 2 trials, as shown in Table 3. For the Safety Analyses, FDA chose to focus on the population of 526 patients with multiple myeloma who were enrolled on Phase 2 studies and the 266 patients who were enrolled on Study 3, the primary efficacy study. Data from the Phase 1 studies were not included in the Agency safety analysis. The inclusion of such data from patients from Phase 1 studies would have introduced a wide range of drug exposures and treatment durations.

**Table 3. Clinical Trials Contained in the Integrated Summary of Safety**

<b>Trial</b>	<b>Phase</b>	<b>Patients (All)</b>	<b>Patients (MM*)</b>
PX-171-001	1	29	10
PX-171-002	1	48	28
PX-171-003 Part 1	2	46	46
PX-171-003 Part 2	2	266	266
PX-171-004 Part 1	2	35	35
PX-171-004 Part 2	2	129	129
PX-171-005	2	50	50
PX-171-006	1b	40	40
PX-171-007	1b/2	108	8
PX-171-008	1b	17	0
<b>Total</b>		<b>768</b>	<b>612 (86 P1 + 526 P2)</b>

\*MM=multiple myeloma

### **Cardiac Adverse Events**

Cardiac on study deaths occurred in a number that was higher than other organ specific causes of on study deaths. The conditions that were associated with these on study deaths were: acute coronary syndrome (1), cardiac arrest (3), and cardiac disorder (1). In addition, one patient (3-09-218) who had dyspnea listed as the cause of death by the Applicant, may have died from complications of congestive heart failure. Another patient (3-16-491) who was listed by the Applicant as having died of disease progression may have died of congestive heart failure.

The timing of the on study cardiac deaths in relationship to carfilzomib dosing of these patients identified by the FDA as on study cardiac deaths is summarized below in Table 4. Most of these patients died in Cycle 1 or Cycle 2 and three of these patients died within 2 days of the last dose, indicating a direct toxic effect of carfilzomib on the heart in these patients. Patient 3-15-441 had a cardiac arrest within hours of the last dose. FDA has identified 3 additional patients for which cardiac causes may have been the cause of death. Patient 3-15-432 had two cardiac arrests in the setting of sepsis, 3 days after the last dose of carfilzomib. Patient 3-16-495 had a cardiac arrest 3 days after the last dose of carfilzomib, and Patient 3-16-778 was found dead at home 6 days after the last dose of carfilzomib.

**Table 4. Summary of Cardiac Deaths**

Patient ID	Age (years)	Cardiac History	Death Occurred			Cardiac Syndrome, CHF, or Arrest
			Cycle	Days After Last Dose	Total Doses	
3-08-086	50	CAD/CABG DM ↑lipids	1	18	4	Acute Coronary Syndrome
3-09-218*	65	HTN	2	22	12	CHF
3-09-220	83	CAD ↑lipids	1	3	2	Arrest
3-11-255	66	HTN	4	1	21	Arrest
3-15-441	53	DM ↑lipids	1	<1**	4	Arrest
3-16-491*	72	HTN	1	8	2	CHF
4-06-156	52	↑lipids	1	2	2	Arrest

\*Identified by FDA

\*\*Death occurred within hours of the last dose.

CAD = Coronary artery disease, CABG = Coronary bypass graft, CHF = Congestive heart failure, DM = Diabetes Mellitus, HTN = hypertension, ↑lipids = hyperlipidemia,

Carfilzomib was discontinued for cardiac disorders in 5.7% of the 526 patients with multiple myeloma enrolled in Phase 2 studies. Among these were discontinuations for congestive heart failure in 9 patients and cardiac arrest in 5 patients. In terms of SAEs, 42 patients experienced cardiac related SAEs. Among these, 18 patients had a SAE associated with congestive heart failure (preferred terms: cardiac failure congestive and congestive cardiomyopathy), and 5 patients experienced cardiac arrest.

One-hundred and twenty-three of the 526 patients (23%) experienced one or more cardiac adverse events (note that Applicant analysis indicates 118 of the 526 (22%) patients reported cardiac adverse events). These adverse events included thirty-seven that were Grade 3 and 10 that were Grade 4 or 5.

### **Pulmonary Adverse Events**

Over 70% of patients enrolled in Phase 2 studies reported adverse events associated with the respiratory system. Twenty-two patients discontinued carfilzomib because of a respiratory adverse event. Dyspnea and pneumonia were the most frequent pulmonary adverse events leading to carfilzomib discontinuations. There were 36 pulmonary SAEs. Reversible SAEs involving the lung were reported in 8 patients, which required hospitalization in 2 patients for stabilization. Two of these events were associated with the clinical diagnosis of pulmonary hypertension (one of which was also associated with veno-occlusive disease and the other with congestive heart failure). Of these 10 patients,

carfilzomib was interrupted in 3, the dose was reduced in 1 and carfilzomib was discontinued permanently in 2.

Dyspnea was a common adverse event and was found in 35% or 186 patients, (FDA analysis) of the 526 multiple myeloma patients entered onto Phase 2 trials. (Note that the Applicant reported 222 patients as experiencing dyspnea). The median duration of these events was 8 days. While most of these events were Grade 1 and 2 in severity, 5% were Grade 3 or 4. It is not clear whether dyspnea was associated with pulmonary toxicity, cardiac toxicity, or infusion reactions because these were single arm trials.

Since there is no control group in the studies presented by the Applicant, it is not possible to isolate the effects of carfilzomib on the different organs from patient and disease related factors. It is remarkable that cardiac and pulmonary toxicities were also reported in the pre-clinical toxicity studies of carfilzomib carried out by the Applicant. The pathogenesis of these cardiac and pulmonary toxicities is unknown. Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m<sup>2</sup> based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. (Note that the bolus infusion may have been administered in a shorter time (20 seconds) than was the case in the bolus infusion in human subjects, which was 2-10 minutes). The studies of repeated intravenous bolus administrations of carfilzomib at  $\geq 2$  mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular and pulmonary systems. Following repeated bolus intravenous administration in monkeys at  $\geq 1$  mg/kg/dose cardiovascular toxicities included myocardial degeneration, myocyte hypertrophy and inflammation. The Applicant reported that use of a 30 minute infusion, rather than the 2-10 minute bolus infusion reduced the mortality seen with carfilzomib in rats. (Note: this report of pre-clinical toxicology was excerpted directly from the Non-clinical Pharmacology/toxicology review).

### **Hepatic Adverse Events**

Among the 526 patients with multiple myeloma who were entered in Phase 2 trials, and among the 266 patients on Study 3, there were two on-study deaths associated with hepatic failure. Both of these individuals had normal liver function tests before being treated with carfilzomib. There were two other life threatening cases of hepatic failure which in contrast to the above two cases, were reversible, one in a 61 year old who experienced grade 2 hepatic encephalopathy and grade 3 hepatic enzyme elevations from days 47-61 of carfilzomib therapy. In Study 3, 42.1% of patients experienced Grade 1-2 elevations in ALT, and 3.6% of patients experienced Grade 3 elevations of ALT.

### **Infusion Reactions with Carfilzomib**

During the course of carfilzomib drug development, the Applicant identified symptoms and adverse events which occurred within 24 hours of each administration of carfilzomib. These adverse events include: fever, chills, rigors, myalgias, arthralgias, dyspnea, hypotension, hypoxia and flushing. In an attempt to reduce this toxicity, the Applicant modified the clinical protocols by adding premedication with dexamethasone along with

the administration of oral and intravenous hydration with each carfilzomib administration during the first two cycles, and thereafter at the investigator's discretion. In addition, the first carfilzomib dose was always 20 mg/m<sup>2</sup> either for the first cycle or later on for the first two doses of Cycle 1. Even with pre-medication, 10% or more of patients develop systemic infusion reactions. The etiology for this constellation of symptoms is unknown and needs to be further characterized in order to adequately inform practitioners intending to use carfilzomib in the treatment of patients with multiple myeloma.

### **Safety**

The safety data suggests that there are a small number of patients with relapsed multiple myeloma who develop life-threatening cardiac toxicities due to carfilzomib. Cardiac toxicity was prominent among "On Study Deaths", adverse events contributing to discontinuation of carfilzomib, SAEs, and adverse events. In addition to the cardiac toxicities, there were significant pulmonary, and to a lesser extent hepatic toxicities and toxicities associated with carfilzomib infusion that need further characterization.

## **9. Advisory Committee Meeting**

Recommended Accelerated Approval (11 in favor, 1 abstention, 0 opposed)

## **10. Pediatrics**

There is no pediatric indication which corresponds to Multiple Myeloma. Therefore, the pediatric issues are not being pursued.

## **11. Other Relevant Regulatory Issues**

- **Application Integrity Policy (AIP):** No Issues
- **Exclusivity or Patent Issues of Concern:** None
- **Financial Disclosures:** Adequate and complete.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:**

Three clinical sites as well as the Applicant site were inspected:

1. Sagar Lonial, M.D., Ph.D. /Site #11 Atlanta, GA

2. David Siegel, M.D./Site #15 Hackensack, NJ
3. Ravi Vij, M.D. /Site #18 St. Louis, MO
4. Applicant 4. Onyx Pharmaceuticals, Inc. San Francisco, CA

### **OSI Overall Assessment of Findings and Recommendations**

For this Phase 2 open-label, single-arm study, three domestic clinical investigator sites and the application Sponsor were inspected in support of this application for Study Protocol PX-171-003. The regulatory deficiencies observed for Sagar Lonial, M.D. (Site #11), David Siegel, M.D. (Site #15) and Ravi Vij, M.D. (Site #18) appeared to be isolated, sporadic, minor or not critical in nature. Sponsor regulatory deficiencies were also considered minor and the Sponsor is in the process of implementing their corrective action plans. Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication. (Note: this section was excerpted directly from the OSI review).

- **Other discipline consults:** None
- **Any other outstanding regulatory issues:** None

## **12. Labeling**

Labeling has been agreed upon by the FDA and the Applicant.

## **13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action: Approval under Subpart H.
- Risk Benefit Assessment

### **Efficacy as Measured by the Primary Endpoint: ORR**

The ORR to carfilzomib in 299 patients with relapsed multiple myeloma who were entered onto the pivotal trial was 22.9%, whether analyzed by the Applicant or by the FDA.

### **Safety**

The safety data suggests that there are a low percentage of patients with relapsed multiple myeloma who develop life-threatening cardiac toxicities due to carfilzomib. Cardiac toxicity was prominent among “On Study Deaths”, adverse events contributing to discontinuation of carfilzomib, SAEs, and adverse events. In addition to the cardiac toxicities, there were significant pulmonary, and to a lesser extent hepatic toxicities and toxicities associated with carfilzomib infusion that need further characterization. As these safety signals were identified using data from a single arm study, it is not possible to

distinguish whether these adverse events arose from carfilzomib, the patient population or the prior treatment history of these patients.

**Benefit Risk Assessment:**

Since carfilzomib produced an ORR of 22.9% in the primary efficacy study, in a population of patients 89% of whom were resistant to bortezomib, and since the Safety Analysis of 526 patients with myeloma entered onto phase 2 trials showed only a low frequency of life-threatening adverse events involving the heart, lung and liver, the benefit-risk is favorable.

**CDTL Recommendation:** The recommendation of the CDTL reviewer is accelerated approval (Subpart H) with the PMRs outlined below.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Commitments

None

- Recommendation for other Postmarketing Requirements

Please see pages 2-5 of this document for a summary of the Postmarketing Requirements.

- Recommended Comments to Applicant

None

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/s/  
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ALBERT B DEISSEROTH  
07/18/2012