CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202714Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	202714
Applicant Name	Onyx Therapeutics, Inc.
Date of Submission	9/27/2011
PDUFA Goal Date	7/27/2012
Proprietary Name / Established (USAN) Name	KYPROLIS/carfilzomib
Dosage Forms / Strength	Vial containing 60 mg of a sterile lyophilized powder for solution injection
Applicant's Proposed Indication(s)	the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Thomas Herndon, M.D./Albert Deisseroth, M.D./Ph.D.
Statistical Review	Kallappa Koti, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Todd Palmby, PhD./J Hayes, Ph.D./ J Bray, Ph.D./Haleh Saber, Ph.D.
CMC Review/OBP Review	W. Michael Adams, Ph.D./Josephine Jee, Ph.D./Janice Brown, M.S./Youngsook Jeon, Ph.D./ Yi Tsong, Ph.D./ Sarah Pope-Miksinski, Ph.D.
Microbiology Review	John Metcalfe, Ph.D./ Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Bahru Habtemariam, Ph.D./Julie Bullock, Pharm.D./Christine Garnett, Ph.D.
DDMAC	James Dvorsky
DSI	Anthony Orencia, M.D./Tejashari Purohit Sheth, M.D.
CDTL Reviews	Albert Deisseroth, M.D., Ph.D.
OSE/DMEPA	Sara K Yee, PharmD/Yelena Maslov, Pharm.D./Kimberly De Fronzo/Irene Z Chan, Pharm.D.
OSE/Epidemiology	
OSE/DRISK	
Other - statistical safety	
Other – Pediatrics Maternal Health Team Other- DCRDP	Elizabeth L. Durmowicz, M.D./Hari C. Sachs, M.D./Lisa Mathis, M.D. Preston M. Dunnmon, M.D./Thomas Marcinzak, M.D./Norman Stockbridge, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Onyx Pharmaceuticals submitted this NDA on September 27, 2011 for carfilzomib for the treatment of patients with relapsed multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent. Carfilzomib is an irreversible proteasome inhibitor administered by intravenous injection. The only approved proteasome inhibitor for the treatment of multiple myeloma is Velcade (bortezomib), a reversible proteasome inhibitor. Velcade has been approved since 2003. Carfilzomib is not approved in any country or region at this time.

The main trial results to support this indication are from a single arm trial enrolling 266 patients with multiple myeloma. This trial was supported by multiple other smaller single arm trials investigating dose/dosing regimen. Given the data, this application could be considered for accelerated approval. The applicant has at least one ongoing large multicenter, randomized controlled trial to demonstrate clinical benefit. This trial is a randomized active controlled trial enrolling patients with multiple myeloma comparing carfilzomib, lenalidomide, dexamethasone with lenalidomide and dexamethasone. The primary endpoint is progression-free survival. This study is being conducted under a Special Procotol Assessment (SPA).

2. Background

The FDA has multiple products approved for use in the treatment of multiple myeloma (newly diagnosed or relapsed) as shown in the table below.

Table 1. FDA Approved Drugs for Multiple Myeloma

Class	Drug	FDA Approval
Alkylating agents	Melphalan Cyclophosphamide	Regular Regular
Anthracyclines	Liposomal doxorubicin (Doxil™)	Regular
Nitrosureas	Carmustine	Regular
ImiDs	Thalidomide Lenalidomide	Accelerated Restricted Distribution (Subpart H)
Proteasome Inhibitors	Bortezomib	Accelerated approval then converted to Regular

Reviewer's Table

Steroids such as prednisone and dexamethasone are frequently used in alone or in combination with the agents in the table above. There is extensive information on the use of these agents in the literature.

3. CMC/Device

Drs. Adams, Jee, and Pope-Miksinski reviewed this application. Ms. Brown has also reviewed this application. The applicant plans to market a single use vial containing sterile injection, powder for lyophilized for solution which is reconstituted with Water for Injection.

The application has an overall recommendation of acceptable based on an EES recommendation dated May 24, 2012. In their reviews they state the following:

The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval with respect to the chemistry, manufacturing, and controls (CMC).

From their review they also state:
The recommended storage conditions are presented in the labeling statements: "Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light."

The stability data appears to provide adequate support for the proposed shelf-life of 18 months or expiration date and the labeling statements for the drug product storage conditions.

From the Statistical Review for stability by Dr. Jeon:
Therefore, the proposed 18-month shelf life of Carfilzomib for Injection is supported by the statistical analysis on long-term stability data.

4. Nonclinical Pharmacology/Toxicology

Drs. Bray, Hawes, Palmby and Saber performed the reviews and did not identify any issues that would preclude approval.

Toxicity signals observed include cardiac toxicity, azotemia, acute phase response, gastrointesintal toxicity, and hematological effects. From their review:
Carfilzomib inhibited the hERG channel potassium current at doses ≥ 1.5 μM. A single bolus intravenous injection of 3 mg/kg carfilzomib in monkeys resulted in increased ventricular premature complex, ST segments and T wave amplitudes in one male, and increased heart rate and troponin-T levels and decreased blood pressure, PR interval, QRS interval and QT interval in the other male tested. Both males administered 3 mg/kg died within 73 hours after dosing.

From their review regarding genotoxicity:

Carfilzomib was not genotoxic in the reverse mutation bacterial test (Ames) and the mouse micronucleus test. Carfilzomib causes an increase in chromosome structural aberrations in human peripheral blood cells at ≥0.04 µg/mL and at ≥2.4 µg/mL in vitro in the absence and presence of metabolic activation, respectively.

The review stated that carfilzomib caused no overt teratogenicity.

5. Clinical Pharmacology/Biopharmaceutics

From the summary section of the Clinical Pharmacology Review:

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 Cmax 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.

Commitment

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.

2) Since PK assessment in the renal impairment study was conducted following carfilzomib doses of 15/20 mg/m2 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/m2 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/m2 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:

 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

 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.

From the review regarding proteasome inhibition:
Dose-dependent inhibition was observed in RBCs and PBMCs after the first dose and appeared to plateau at approximately 75% proteasome inhibition at doses of 11 mg/m2 and above. Following repeat carfilzomib doses, proteasome inhibition was increased to about 90% in both RBCs and PBMCs.

From the review regarding half-life:
Carfilzomib has a very short half life (0.45 to 1 hour), and no drug accumulation is expected following multiple dose drug administration.

From the review regarding protein-binding (PPB):
The mean PPB was 98.0%, 97.6%, 98.3%, 98.2% and 97.9% in patients with normal renal function, mild, moderate, and severe renal impairment, and dialysis subjects, respectively.

From the IRT review by Dr. Earp:
No large change in QTc (i.e., >20 ms) was detected in this trial following administration of carfilzomib (15 mg/m2, 20 mg/m2 and 36 mg/m2).

6. Clinical Microbiology

A product quality Microbiology review by Dr. Metcalfe recommended approval.

7. Clinical/Statistical-Efficacy

The main trial enrolled 266 patients with relapsed multiple myeloma. Patients enrolled had a median age of 63 and 58% were male. The majority of patients were white (71%) with a smaller percentage of patients who were black (20%). All other

racial/ethnic categories were less 10%. The majority had a good performance status (87%). Their disease characteristics included 60% normal or favorable cytogenetics and 67% beta-2 microglobulin level < 5.5 mg/L. Patients had received a mean of 5.4 prior therapies with 74% of patients had undergone an autologous transplant. Approximately 95% of patients had disease characterized as “refractory” to their most recent therapy by protocol definition. The applicant’s response rate (complete and partial responses) was 22.9%. The applicant used an independent review committee.

The Division review team performed a number of exploratory analyses based on exposure to prior therapy. Regardless of prior therapy exposure, the response rate was in the low 20% range.

The Applicant’s duration of response was 7.8 months and based on first response to progression. The review team analyzed response based on response to last date of confirmation of same status and obtained 6.5 months.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy.

8. Safety

Adverse events observed during the trial included myelosupression (anemia, neutropenia, thrombocytopenia), general disorders (e.g., fatigue, asthenia), gastrointestinal (nausea, vomiting, diarrhea), pulmonary (e.g., cough, upper respiratory infection), neurologic (e.g., pain), musculoskeletal, and electrolyte/laboratory (e.g., creatinine, glucose, sodium, phosphorus, calcium).

During the review, the review team identified several areas for particular review: cardiovascular events, hepatotoxicity, and pulmonary toxicity.

The difficulty with the safety review from single arm trials is that it is difficult to state with certainty whether the adverse reactions observed are attributable to the drug, underlying (non-myeloma disease), or prior therapy.

Cardiac Adverse Events
Deaths during the first 30 days: The most common non-myeloma cause was cardiac events including sudden death, myocardial infraction, arrest, and congestive heart failure.

Most common cause of treatment discontinuation excluding disease progression: cardiac.

Hepatotoxicity
Two patients who enrolled in the trials with normal liver enzymes died after they were treated with carfilzomib and developed liver enzyme elevations/failure. Other patients experience liver enzyme elevation although they did recover. No Hy’s Law cases were identified.

Pulmonary
The second common cause of treatment discontinuation excluding disease progression: pulmonary (dyspnea and pneumonia). Two patients developed pulmonary arterial hypertension.

Infusion Reactions with Carfilzomib
During the course of carfilzomib drug development, the Applicant identified symptoms and adverse events which occur within 24-48 hours of administration of carfilzomib. These adverse events include: fever, chills, rigors, pyrexia, 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. The amount of dexamethasone per cycle was 24 mg (4 mg per treatment) and much lower than low dose dexamethasone given in other multiple myeloma treatment regimens. This 4 mg pre-carfilzomib dexamethasone dose was not completely successful at preventing infusion reactions.

Comment: Due to the safety concerns raised by the reported cardiac and pulmonary adverse reactions during the main phase 2 trial, we requested and reviewed a tabular summary of the most recent DSMB adverse event report. The report did not suggest a reason to close the ongoing phase 3 trials for safety.

Comment: Due to the seriousness of certain adverse reactions (cardiac, pulmonary, etc.) the labeling will recommend that carfilzomib treatment be withheld. Retreatment should be based on resolution of signs and symptoms and physician discretion.

9. Advisory Committee Meeting

This product was discussed at a Oncologic Drugs Advisory Committee meeting on June 20, 2012. The Committee voted 11 (yes) to 1 (abstain) that the available clinical data demonstrate a favorable risk-benefit profile for carfilzomib.

10. Pediatrics

N/A- Orphan designation

11. Other Relevant Regulatory Issues

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

The Office of Scientific Investigation conducted audits at 3 clinical sites and found the data to be reliable.

The applicant has more than one phase 3 trial which could be used to provide evidence of clinical benefit.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff. Krypolis is acceptable to OSE.

13. Decision/Action/Risk Benefit Assessment

Recommended regulatory action - Approval for the treatment of patients with relapsed multiple myeloma

The applicant has agreed to submit the complete study report and datasets for the ongoing ASPIRE trial (PX-171-009). This trial is a randomized active controlled trial enrolling patients with multiple myeloma comparing carfilzomib, lenalidomide, dexamethasone with lenalidomide and dexamethasone. The primary endpoint is progression-free survival.

This study protocol is being conducted under a Special Protocol Assessment and the study has completed accrual. The Applicant estimates the submission date as June 2014.

Risk Benefit Assessment
The risk benefit assessment suggests that carfilzomib is effective for the treatment of patients with multiple myeloma whose disease has relapsed after receiving established and approved treatments such as bortezomib, lenalidomide, thalidomide, mephalan and other alkylating agents. The most common side effects include: fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. The following adverse reactions were identified as being particularly concerning: cardiac, pulmonary, hepatic, thrombocytopenia, and infusion reactions. The latter list is included in the warnings and precautions section of the labeling. Additionally the cardiac and pulmonary will be the subject of ongoing PMRs under FDAAA.

Recommendation for Post marketing Risk Management Activities
Routine post-marketing surveillance except for enhanced pharmacovigilance for cardiac adverse reactions, pulmonary adverse reactions, hepatoxicity

Cardiac and pulmonary testing will be incorporated into a planned phase 3 trial in order to better understand the potential cardiac and pulmonary risks of carfilzomib.

Recommendation for other Post marketing Study Requirements/ Commitments

We have asked the applicant:

to evaluate the effect of hepatic impairment
to evaluate the effect of renal impairment (i.e., mild, moderate, severe)
using a different dosing regimen (over 30 minutes)

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
07/20/2012