

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202714Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Management Options Review Options Review

Date: July 12, 2012

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Drug Name(s): Carfilzomib (Krypolis, PX-171)

Therapeutic Class: Second generation proteasome inhibitor

Dosage and Route: Lyophilized powder 60 mg per vial

Application Type/Number: NDA 202714

Submission Number: 1

Applicant/sponsor: Onyx Pharmaceuticals

OSE RCM #: 2012-1511

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1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) Krypolis (carfilzomib, PX-171). On January 31, 2011 the Division of Hematology Products (DHP) received a new drug application (NDA) from Onyx Pharmaceutical for Krypolis (carfilzomib, PX-171) with a proposed indication for 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.

The applicant is seeking approval on the basis of a single, open-label, single arm, phase 2 trial that included 266 patients with relapsed, refractory multiple myeloma who previously received two or more lines of therapy. The applicant did not submit a proposed REMS or risk management plan.

2 BACKGROUND

Carfilzomib is a second generation proteasome inhibitor which forms an irreversible, covalent bond that inhibits the chymotrypsin-like activity of the 20S proteasome. Inhibition of proteasome-mediated proteolysis results in a build-up of polyubiquitinated proteins, which interferes with intracellular protein homeostasis resulting in cell cycle arrest, apoptosis and inhibition of tumor growth. Multiple myeloma (MM) cells are reported to be sensitive to proteasome inhibitors.

3 REGULATORY HISTORY

Carfilzomib is a new molecular entity, orphan drug designation was granted in 2008. It not approved or marketed in the United States or any other country. Onyx requested approval under 21 CFR 314.510, Subpart H accelerated approval, approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

Bortezomib (Velcade), a reversible first-in-class proteasome inhibitor, was approved (full approval) in 2003 and is indicated for the treatment of patients with for MM and treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. Bortezomib was approved without risk mitigation strategies.

Bortezomib is the only approved agent in the same drug class as carfilzomib.

4 MATERIALS REVIEWED

- Herndon T.M. Clinical Review of NDA 202714 (carfilzomib) entered in DARRTS June 19, 2012
- FDA Briefing Document for the June 20, 2012 Oncologic Drugs Advisory Committee (ODAC) for NDA 202714 Carfilzomib (Krypolis)

- Product labeling Sequence 0030, received June 29, 2012

4 REVIEW OF RISK MANAGEMENT OPTIONS

4.1 APPLICANTS PROPOSED RISK EVALUATION AND MITIGATION STRATEGY

The sponsor did not submit a risk evaluation and mitigation strategy (REMS) or a risk management plan with the NDA.

4.2 OVERVIEW OF CLINICAL PROGRAM

The applicant is seeking approval on the basis of a single, open-label, single arm, phase 2 trial (PX-171-003-A1) that included 266 patients with relapsed, refractory MM who previously received two or more lines of therapy. The proposed dosing schedule for carfilzomib is 20 mg/m² injection (cycle 1) and 27 mg/m² injection (cycle \geq 2) on Days 1, 2, 7, 8, 15 and 16 of a 28-day cycle.

PX-171-003-A1 studied patients with relapsed and refractory advanced MM who had previously been treated with bortezomib (a first-generation proteasome inhibitor; 99%) and either thalidomide (74%) or lenalidomide (93%). In addition, patients had exhausted other available therapies including alkylators (e.g., cyclophosphamide, melphalan) and steroids (e.g., prednisone, dexamethasone). Approximately 60% had prior anthracyclines (e.g., doxorubicin) and/or hematopoietic stem cell transplantation (74%). The median number of prior therapies was 5 with a range of 1-20. In addition, 252 of 266 patients treated after Amendment 1 of PX-171-003-A1 had documentation of refractoriness to their last prior therapy, a dismal prognosis, and no clinically meaningful treatment options. Many patients suffered from the effects of prior treatment including ongoing peripheral neuropathies, renal insufficiency or renal failure, cardiac complications, recurrent infections, corticosteroid toxicity, and other end-organ dysfunction making treatment of their MM restricted to supportive care measures as they would not be able to tolerate toxic chemotherapy.

The overall response rate to carfilzomib was 22.9%.¹ The estimated median duration of response is 6.5 months (CI 95%, 4.6, 8.3).

The medical officer's clinical review states that this overall response rate is acceptable for a new therapy for MM based on response rates of current therapies in heavily pretreated patients.

¹ Overall response rate is defined as stringent Complete Response, Complete Response, Very Good Partial Response, or Partial Response according to the International Uniform Response Criteria for Multiple Myeloma assessment criteria. Durie BGM, Harousseau JL, Miguel JS, et al. International response criteria for multiple myeloma. *Leukemia* 20:1467-1473, 2006.

4.2 SAFETY

The safety database for carfilzomib includes 768 patients from phase 1 and phase 2 trials that include patients with diseases other than MM. For the safety analyses the Dr. Herndon focused on 526 patients with MM who were enrolled in PX-171-003-A1 or other phase 2 studies. The most frequent cause of on-study death was attributed to progression of disease. Major safety concerns identified include serious cardiac, respiratory, and hepatic adverse events.

- Cardiac: Although the numbers are small, the sponsor attributed 5 deaths to cardiac adverse events; the agency identified an additional 2 patients with deaths associated with cardiac adverse events and an additional 3 patients where cardiac adverse events possibly contributed to death. Cardiac adverse events contributed to on-study deaths, other serious adverse events, and discontinuations of carfilzomib.
- Respiratory: Dyspnea was the most frequent pulmonary adverse event leading to discontinuation of carfilzomib and the most frequent pulmonary SAE. Dr. Herndon states in his review that over 70% of the patients enrolled in the Phase 2 trials experienced respiratory adverse events. Dyspnea was reported in 35% of the 523 of the patients with MM; with 5% of the cases reported as grade 3 or 4.
- Hepatic: There were a total of two on-study deaths associated with hepatic failure reported from the Phase 2 trials and PX-171-003-A1 study, and three cases of hepatic failure that were reversible. There were no Hy's Law cases.

It is important to note that data are from single arm studies with no comparator/placebo arm(s) data available. Therefore, it is not possible to establish causality. As Dr. Herndon states, "in general, the cause of adverse events from single arm trials where the drug effect is unknown must be assigned to the experimental therapy."

Pregnant or lactating women were excluded from participating in the clinical trials. Patients had to agree to use adequate contraception. The mean age in patients enrolled in PX-171-003-A1 was 62.9 years (range 37-87yrs; ~40% female). Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose, there are no adequate and well-controlled studies in pregnant women.

4.3 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

Study PX-171-009 is a phase 3 trial and has been initiated to confirm the clinical benefit seen in the phase 2 trials. This is a 700-patient, multicenter, international, randomized, open-label study of lenalidomide with low-dose dexamethasone (Rd) versus carfilzomib + Rd (CRd) with progression free survival as the primary endpoint in patients with relapsed or refractory MM after 1–3 prior therapies. Study PX-171-009 was supported by FDA under a Special Protocol Assessment, this trial will serve as the confirmatory trial in support of the accelerated NDA approval.

In addition, Onyx Pharmaceuticals will be required to fulfill postmarketing requirements that identify and characterize the cardiac, and pulmonary toxicities associated with carfilzomib, and evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m² in patients with multiple myeloma.

4.4 ODAC

The ODAC convened on June 20, 2012 to consider this application. ODAC was asked to vote on the following question, “Is the risk benefit assessment favorable for the use of carfilzomib in 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?” Eleven members voted in favor and one member abstained. Risk management was not discussed.

5 DISCUSSION

Dr. Herndon’s review states that the benefit of the overall response rate observed with carfilzomib in a heavily pretreated patient population with a universally fatal disease who have limited to no other treatment options outweighs the serious and potentially life threatening adverse events.

Cardiac adverse events and adverse events associated with the respiratory organ system and to, a lesser extent, the hepatobiliary system requires further characterization. These safety signals were identified using data from a single arm study, it is not possible to differentiate their association with carfilzomib, multiple myeloma, or the treatment history of the heavily pretreated patients enrolled in these studies.

The only other approved proteasome inhibitor is bortezomib, a first-generation proteasome inhibitor approved in 2003. Bortezomib lists cardiac disorders, pulmonary disorders, and hepatic events and advise women of childbearing potential to avoid becoming pregnant because of the potential for fetal harm in the Warnings and Precautions section of product labeling, with no Boxed Warning and no further required risk management measures.

It is expected that the Phase 3 trial and post marketing requirements will assist in characterizing the adverse event profile. If serious adverse events can be characterized specific risk mitigation strategies can be considered. Based on the limited safety information and in comparison to bortezomib risk/benefit profile there is no precedence to require additional risk management measures for carfilzomib.

6 CONCLUSION

Labeling in conjunction with post-marketing requirements to further evaluate carfilzomib’s benefits and risks is a reasonable strategy and is consistent with bortezomib, a first-generation proteasome inhibitor used for the similar indication. Krypolis (carfilzomib, PX-171) can be approved without REMS.

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/s/

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