

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205552Orig2s000

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

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
RISK EVALUATION AND MITIGATION STRATEGY REVIEW**

Date: September 17, 2013

Reviewer(s) Joyce Weaver, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)

Team Leader Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Division Director: Claudia Manzo, Pharm.D., Director, DRISK

Subject: Review to determine if a REMS is necessary

Drug Name(s): Imbruvica (ibrutinib)

Therapeutic class & dosage form: Tyrosine Kinase Inhibitor
140mg capsules

OND Review Division Division of Hematological Products

Application Type/Number: NDA 205552

Application received June 28, 2013

PDUFA/Action Date February 28, 2014

Applicant/sponsor: Pharmacyclics, Inc

OSE RCM #: 2013-1057

TSI #: n/a

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1 INTRODUCTION

This review by the Division of Risk Management evaluates if a Risk Evaluation and Mitigation Strategy (REMS) is needed for the tyrosine kinase inhibitor, ibrutinib. The proposed indications for ibrutinib include treatment of patients with of previously treated mantle cell lymphoma (MCL) and previously treated chronic lymphocytic lymphoma (CLL).

Pharmacyclics, Inc did not submit a Risk Evaluation and Mitigation Strategy (REMS) or risk management plan ibrutinib.

1.1 BACKGROUND

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor. Pharmacyclics, Inc has submitted an application to the Agency for the treatment of previously treated MCL and CLL.

1.2 REGULATORY HISTORY

Pharmacyclics, Inc submitted an application June 28, 2013 to the FDA for ibrutinib, a BTK inhibitor, for the following proposed indications:

- Treatment of patients with MCL who have received at least one prior therapy.
- Treatment of patients with CLL who have received at least one prior therapy.

The following are regulatory milestones pertinent to the application:

- October 29, 2012—The Agency granted Fast Track designation for ibrutinib for the treatment of patients with CLL.
- December 18, 2012—The Agency granted Fast Track designation for ibrutinib for the treatment of patients with MCL.
- February 8, 2013— The Agency granted Breakthrough Therapy designation for ibrutinib for the treatment of patients with MCL
- June 28, 2013—last module of the NDA received
- August 27, 2013—NDA filed; filing communication sent to sponsor accepting the application for review, and granting priority review.

Although the PDUFA goal date for the application is February 28, 2014, the division has set an internal goal action date of October 27, 2013. Both indications are being considered for subpart H accelerated approval.

2 MATERIALS REVIEWED

We reviewed the following:

- Application submitted June 28, 2013.

- FDA's fast track and breakthrough therapy determinations and notifications
- Minutes from April 9, 2013 type B meeting
- Sponsor's slides from NDA Orientation Meeting, July 12, 2013
- Discipline handouts and slides from mid-cycle meeting for NDA 205552, meeting held August 14, 2013.
- NDA Safety Update, August 19, 2013
- Sponsor responses to clinical inquiries (including inquiry regarding bleeding events), August 18, 2013
- FDA-edited draft labeling, edited as of September 16, 2013.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM¹

Mantle cell lymphoma

The data submitted in support of the MCL indication were derived from a single-arm, multi-center, Phase 2 trial in 111 patients with MCL. Forty-eight of the 111 patients had prior treatment with bortezomib; the remaining 63 patients did not have previous treatment with bortezomib. Patients were dosed with ibrutinib 560 mg orally once daily. The primary endpoint was overall response rate. Over 67% of patients responded to treatment. The median duration of response was about 16 months.

The most frequently reported grade 3 or higher adverse events were neutropenia (experienced by 15% of patients), pneumonia (12%), thrombocytopenia (10%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%). Serious adverse events occurred in 56% of patients, the most frequently occurring serious adverse event was pneumonia (5%). Fifty-nine percent of patients discontinued the trial, most (44%) because of disease progression.

Four percent of patients receiving ibrutinib in the MCL trial experienced grade 3 or higher bleeding events, 49% of patients experienced a bleeding event, and bruising was experienced by 23% of the patients. There were no fatalities secondary to bleeding.

Chronic lymphocytic leukemia

The data submitted in support of the CLL indication were derived from a dose-finding multi-center trial in 133 patients. Patients included the following cohorts: **relapsed/refractory disease receiving 420 mg daily (27 patients)**, treatment-naïve patients at least 65 years old receiving 420 mg daily (26), relapsed/refractory disease receiving 840 mg daily (34 patients), treatment-naïve patients at least 65 years old receiving 840 mg daily (5), **relapsed/refractory high-risk patients receiving 420 mg daily (25)**, relapsed/refractory patients receiving 420 mg daily with food (16).

¹ Summary presented here is adapted from the mid-cycle handout, August 14, 2013.

The bolded cohorts, **relapsed/refractory disease receiving 420 mg daily (27 patients) and relapsed/refractory high-risk patients receiving 420 mg daily (25)** were included in the efficacy analysis. In the cohorts analyzed for efficacy, 38/48 patients (79%) responded to the treatment. The 95% confidence interval for the overall response rate was 67.7 – 90.7 months.

Grade 3 or 4 adverse events included neutropenia, pneumonia, thrombocytopenia, hypertension, dehydration and sinusitis. Serious adverse events occurred in 61% of patients.

Six percent of patients receiving ibrutinib in the CLL trial experienced grade 3 or worse bleeding events, 63% of patients experienced a bleeding event, and 54% of the patients experienced bruising. There were no fatalities secondary to bleeding.

3.2 SAFETY CONCERNS

The most concerning safety issue discovered in the review of the data is bleeding. The sponsor was asked to provide additional information about bleeding events that have occurred with ibrutinib, and to detail their investigation to explore the bleeding signal. The sponsor replied that they have focused mostly on CNS hemorrhagic events, the events that they consider to be the most serious. As of April 6, 2013, nine of the 636 patients in the ibrutinib development program experienced a CNS hemorrhage.

The sponsor concluded that hemorrhage remains an important safety signal for ibrutinib. The sponsor said, the following safety monitoring activities for bleeding events were taken or are continuing (the following is excerpted from the sponsor's Aug 18 summary).

1. External review by hematology and neurology experts of the early case series identified that concomitant use of warfarin and head trauma may be the confounders of the initial clusters of reports of CNS hemorrhagic events.

Reviewer comment: In the 5 major bleeding events that occurred in the trials reviewed for this application, only one patient was receiving warfarin, and head trauma was not reported as a confounder in any case.

2. Major hemorrhage is considered as an Adverse Event of Special Interest. Investigators are instructed to report any new cases to Pharmacyclics within 24 hours. This alert system allows Pharmacyclics to have prompt review of safety data. All new cases of major hemorrhages are reviewed in depth to identify risk factors and concomitant drug use. Platelet counts and coagulation parameters are followed.

Reviewer comment: Unfortunately, this has not elucidated risk factors to guide therapy.

3. Two Dear Investigator Letters were issued provided appropriate education and guidance in the exclusion of warfarin use and the temporary hold of ibrutinib for peri-operative management. This information is part of all clinical studies as well as the draft prescribing information.

Reviewer comment: The guidance was presumptive but was not based on data.

4. Panel of experts in coagulation was assembled to review full safety data, and management guidelines in 2012 and agreed that the current study management was appropriate.

5.

(b) (4)

Reviewer comment: The guidance is not based on data.

6. To mitigate the potential risk of leukostasis where bleeding risk is increased, guidance for patient management has been added to the protocol, Investigator's Brochure, and the draft prescribing information for patients with high circulating malignant cells (>400,000/mcL).
7. Routine aggregate safety surveillance is performed on a regular basis with cumulative data to review trends across studies and this safety concern is part of the ibrutinib Pharmacovigilance Plan for post market surveillance.

Reviewer comment: DHP and the Division of Pharmacovigilance are proposing enhanced pharmacovigilance.

8. Epidemiological data to ascertain background rates of bleeding in this population using the SEER database is ongoing.
9. Future controlled trials data will be available to better understand the background rates of the occurrence of major hemorrhage in this patient population.

Overall, bleeding/bruising events have occurred in 23% and 54% of patients who received ibrutinib in the MCL trial and the CLL trial, respectively. Five patients have had bleeding characterized as a major event. The medical officer identified risk factors (concomitant warfarin use, concomitant dabigatran use, clotting factor deficiency, history of chronic gastrointestinal bleeding) in four of the five patients who had bleeding events. The remaining patient did not have identifiable risk factors for bleeding.

3.3 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The sponsor did not propose a REMS for ibrutinib.

The sponsor's draft labeling includes (b) (4) infections, bleeding, and development of other primary malignancies in the *Warnings and Precautions* section of the labeling. (b) (4)

The clinical trials excluded patients on warfarin after a cluster of bleeding events in a trial, although only one patient who experienced a major bleeding event was taking warfarin concomitantly. (b) (4)

FDA edits to the labeling include placing the bleeding risk as the first issue presented in the *Warnings and Precautions* section of the labeling, and adding potential embryo-fetal toxicity to the *Warnings and Precautions* section of the labeling.

4 DISCUSSION OF A REMS FOR IBRUTINIB

Aside from bleeding events, the adverse reaction profile for ibrutinib appears to be favorable. Because of the overall favorable adverse reaction profile, patients who might not be able to tolerate other chemotherapeutic agents could be prescribed ibrutinib preferentially. This could result in patients at a higher risk of bleeding being prescribed ibrutinib. It would be helpful to prescribers to provide guidance regarding which patients should not receive ibrutinib because of an unfavorable risk–benefit profile. However, data are not available to provide this guidance. At this time, we cannot inform prescribers which patients are at increased risk for bleeding, or how to prevent bleeding events. The mechanism of bleeding with ibrutinib is not known, and there are no data establishing the risk factors that are important to prevent bleeding events. (b) (4)

Using a REMS to prevent patients at higher risk of bleeding from receiving ibrutinib would not be helpful because we cannot identify the important risk factors at this time.

Two postmarketing requirements (PMRs) are being crafted to obtain additional data about the bleeding signal. First, an *in vitro* study will be required to examine the effect of ibrutinib on platelet aggregation. This will include samples from patients with and without concomitant conditions and medications that could impair platelets. The second PMR will require enhanced pharmacovigilance to obtain information about bleeding events that occur in patients receiving ibrutinib. Information from the enhanced pharmacovigilance program will be used to help identify risk factors for bleeding with ibrutinib. The results of both PMRs could guide future safety studies to examine the bleeding signal.

Additionally, clinical trials currently accruing patients will be completed to satisfy the requirements of subpart H. Additional safety data will be submitted with these trial results.

5 CONCLUSION/RECOMMENDATION

Based on the information that is currently available, a REMS with a communication plan or elements to assure safe use for ibrutinib is not recommended. Implementing a REMS for ibrutinib without a better understanding of factors that may contribute to the risk of bleeding may restrict therapy without evidence establishing who is at increased risk for bleeding events, and may create a barrier that prevents patients who could benefit from the drug from receiving it. It would not be appropriate to exclude all patients with risk factors for bleeding from receiving ibrutinib until additional data are available to better understand the bleeding safety signal. A communication plan REMS would not be helpful because there is not a clear message to communicate to prescribers. Better understanding of factors that contribute to increased risk of bleeding are needed to create an effective risk message.

The risk of bleeding should be addressed by describing what is known about the risk in the labeling for ibrutinib. As additional data become available, the utility of implementing a REMS can be better appreciated.

We ask that DHP include DRISK in future discussions regarding this safety signal.

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/s/

JOYCE P WEAVER
09/17/2013

CLAUDIA B MANZO
09/17/2013
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