# 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 EVAULATION AND MITIGATION STRATEGY REVIEW**

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| Date: | September 17, 2013 |
| Reviewer(s) | Joyce Weaver, Pharm.D., Risk Management Analyst<br>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 &<br>dosage form: | Tyrosine Kinase Inhibitor<br>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 PROGRAM[1]

### 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.

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