CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER 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

Pharmacovigilance Memo

Date:	March 14, 2014
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Division Director:	Scott Proestel, MD DPV II
Product Name:	Imbruvica (ibrutinib)
Subject:	Type B meeting response
Application Type/Number:	NDA 205552
Applicant/Sponsor:	Pharmacyclics, Inc.
OSE RCM #:	2014-148

1 INTRODUCTION

The Division of Pharmacovigilance II (DPV II) was asked by the Division of Hematology Products (DHP) to provide a response to Question 12 posed by Pharmacyclics, Inc. in their Type B (Pre-supplemental NDA) meeting package. The purpose of the Type B Pre-supplemental NDA meeting is to discuss the efficacy and safety analysis data from the Phase 3 study PCYC-1112-CA in support of regular (full) approval of ibrutinib as monotherapy for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who have received at least one prior therapy. Additionally, Pharmacyclics would like to discuss the content of the proposed supplemental NDA (sNDA) including: the collective clinical efficacy and safety data in support of the sNDA filing. Specifically pertaining to DPV II, Pharmacyclics would like to discuss and obtain agreement with the Agency on the proposed update to the pharmacovigilance plan.

1.1 BACKGROUND

Imbruvica is a Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.[1] Imbruvica was FDA-approved November 13, 2013.

Atrial fibrillation is a labeled adverse event found in the following sections of the ibrutinib label:[1]

Section *6 Adverse Reactions*
Subsection *6.1 Mantle Cell Lymphoma* and *6.2 Chronic Lymphocytic Leukemia*

Section *8 Use in Specific Populations*
Subsection *8.5 Geriatric Use*

On August 26, 2013, Pharmacyclics, Inc. submitted a pharmacovigilance plan as requested by FDA on August 8, 2013. On February 5, 2014, Pharmacyclics, Inc. submitted a Type B Pre-supplemental NDA meeting package for the upcoming March 12, 2014 Type B meeting with FDA. Pharmacyclics, Inc. provided the following question and rationale that was referred to DPV II for a response:

> ***Question 12***
> ***Is the proposed update to the pharmacovigilance plan acceptable to the FDA?***
>
> *Based on the available safety data on PCYC-1112-CA, atrial fibrillation has been identified as a new important potential risk compared to the pharmacovigilance (PV) plan in the original NDA dated 23 August 2013. The original PV plans includes the following risk and potential risks:*
>
> ***Important Identified Risk***
> *Leukostasis*

Important Potential Risks
Infections
Hemorrhage
Hypersensitivity
Other malignancy
Drug-drug interaction
Teratogenicity

Other potential area of safety information:
Off-label use
Medication errors, overdose, and accidental exposure

New Important Potential Risk: Atrial fibrillation

The following activity is proposed:
1. *Routine pharmacovigilance (ongoing/post-marketing): Targeted surveillance with use of a guided collection form to obtain additional clinical and diagnostic information related to atrial fibrillation.*
2. *Additional PV (for ongoing clinical studies): Case series analyses on controlled studies to clarify background incidence.*

2 RESULTS AND DISCUSSION

On March 2, 2014, DPV II searched the FDA Adverse Event Reporting System (FAERS) database utilizing the higher level term (HLT) supraventricular arrhythmias to identify cases of atrial fibrillation or atrial flutter with ibrutinib since the approval date of November 13, 2013. After removing duplicates, the search retrieved 11 cases of atrial fibrillation (8) and atrial flutter (3). All 11 cases reported a primary serious outcome of hospitalization (10) or other medically serious outcome (1). All 11 cases were either confounded by concomitant medications labeled for an association with atrial fibrillation or cardiac arrhythmia (10) or provided limited information to assess the case (1).

DPV II agrees with the sponsor's addition of atrial fibrillation to the PV plan based on the available information.

3 REFERENCES

[1] Imbruvica (ibrutinib) [package insert]. Pharmacyclics, Inc. Sunnyvale, CA. Label issued November 2013.

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/s/

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