

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205552Orig2s000

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

Safety Evaluator: Katherine Coyle, PharmD, BCPS
Division of Pharmacovigilance II (DPV II)

Team Leader: Tracy Salaam, PharmD
DPV II

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/

KATHERINE M COYLE
03/14/2014

TRACY M SALAAM
03/14/2014

SCOTT E PROESTEL
03/14/2014

PMR/PMC Development Template PMR 2122-2

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 205552
Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

PMR Description: Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 578 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Completed
		(September /2013)
	Trial Completion:	July 2016
	Final Report Submission:	November 2016
	Other: _____	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Relapsed or refractory chronic lymphocytic leukemia (CLL) is a life-threatening condition. Although most patients who undergo chemotherapy for CLL achieve an initial response, disease relapse invariably occurs. The median progression free-survival varies according the subsequent treatment regimen, with reported median PFS for FCR, FR, and single-agent fludarabine of 52 months, 42 months, and 18 months, respectively.

In the single-arm clinical trial PCYC-1102-CA, the applicant reports a 58% overall response rate in 48 patients with relapsed or refractory CLL. The duration of response ranged from 5.6 to 24.2+ months. The median DOR was not reached.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The Agency has previously accepted overall response rates supported by duration of response from a single-arm clinical trial as a basis for initial approval.

The goal for this PMR would be to obtain long-term efficacy outcomes including progression-free survival from a randomized clinical trial. Time-to-event endpoints cannot be adequately interpreted in single-arm clinical trials due to confounding effects of the natural history of the disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: Submit the clinical study report and data from the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Confirmatory clinical trial under subpart H
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

RCK

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/s/

DIANE C HANNER
02/11/2014

ROBERT C KANE
02/11/2014

PMR/PMC Development Template PMR 2122-1:

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 205552
Product Name: IMBRUVICA, PCI-32765 (ibrutinib) capsules, 140 mg

PMR Description: Submit the results of the completed randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 391 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

PMR Schedule Milestones:	Final Protocol Submission:	Completed (January 2014)
	Trial Completion:	Completed (January 2014)
	Final Report Submission:	June 2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
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- Other

Relapsed or refractory chronic lymphocytic leukemia (CLL) is a life-threatening condition. Although most patients who undergo chemotherapy for CLL achieve an initial response, disease relapse invariably occurs. The median progression free-survival varies according the subsequent treatment regimen, with reported median PFS for FCR, FR, and single-agent fludarabine of 52 months, 42 months, and 18 months, respectively.

In the single-arm clinical trial PCYC-1102-CA, the applicant reports a 58% overall response rate in 48 patients with relapsed or refractory CLL. The duration of response ranged from 5.6 to 24.2+ months. The median DOR was not reached.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The Agency has previously accepted overall response rates supported by duration of response from a single-arm clinical trial as a basis for initial approval.

The goal for this PMR would be to obtain long-term efficacy outcomes including progression-free survival from a randomized clinical trial. Time-to-event endpoints cannot be adequately interpreted in single-arm clinical trials due to confounding effects of the natural history of the disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

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Required

- Observational pharmacoepidemiologic study
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RCK _____
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/s/

DIANE C HANNER
02/11/2014

ROBERT C KANE
02/11/2014

REGULATORY PROJECT MANAGER LABELING REVIEW
Division of Hematology Products (DHP)

Application: 205552-Original #2

Name of Drug: Imbruvica[®] (ibrutinib) capsules, 140 mg.

Applicant: Pharmacyclics, Inc.

Labeling Reviewed

Submission Date: January 9, 2014

Receipt Date: January 9, 2014

Background and Summary Description:

The NDA 205552-Original #1 was approved on November 13, 2013, for Mantle Cell Lymphoma (MCL) that has received at least one prior therapy.

The NDA was initially received on June 28, 2013, and it was split on October 11, 2013, in order to accommodate taking an earlier action on Original #1 Mantle Cell Lymphoma.

This new drug application – Original #2 provides for the use of Imbruvica[®] (ibrutinib) capsules, 140 mg for the treatment of patients with Chronic Lymphocytic Leukemia (CLL) that have received at least one prior therapy.

Review

This review is based on the applicant's submitted word format of the PI. The proposed PI was compared to the (11/13/13) Mantle Cell Lymphoma –Original #1 currently approved PI. This was done to ensure that all the changes were shown as track changes to allow for an appropriate review of the PI. The following changes have been identified as follows: Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines. The following revisions were noted.

The labeling meetings for Chronic Lymphocytic Leukemia (CLL) –Original #2 have been scheduled for January 16, 23, 27, and February 4, 2014, at which time the clinical team will be reviewing the PI.

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/s/

DIANE C HANNER
02/04/2014

MONSURAT O AKINSANYA
02/04/2014

**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: January 31, 2014

Team Leader: Tracy Salaam, PharmD
Division of Pharmacovigilance II (DPV II)

Division Director: Scott Proestel, MD
DPV II

Product Name: Imbruvica (ibrutinib)

Subject: CLL Indication and PMR 2060-4

Application Type/Number: NDA 205552

Applicant/Sponsor: Pharmacyclics, Inc.

OSE RCM #: 2014-281

1 INTRODUCTION

The Division of Pharmacovigilance II (DPV II) was asked by the Division of Hematology Products (DHP) to provide a memo regarding whether DPV recommends applying the postmarketing requirement (PMR) 2060-4, approved under the mantle cell lymphoma (MCL) indication for Imbruvica (ibrutinib), to the proposed indication of chronic lymphocytic leukemia (CLL), which is presently under review by FDA.

1.1 BACKGROUND

Imbruvica is a Bruton's kinase inhibitor indicated for the treatment of patients with MCL who have received at least one prior therapy.¹ Imbruvica was FDA-approved November 13, 2013 under Fast Track designation, priority review, and accelerated approval, as a first-in-class breakthrough therapy with orphan drug status.

In the approval letter, FDA determined that among other postmarketing requirements (PMRs), the sponsor was required to conduct the following²:

PMR 2060-4

Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs. Major hemorrhagic events are defined as any one of the following:

I. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,

II. Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells,

III. Bleeding resulting in a serious adverse drug experience [as per 21 CFR 314.80(a)]

This enhanced pharmacovigilance study will include:

1. Targeted and expedited surveillance with a guided collection form (as referenced in Pharmacyclics' Pharmacovigilance Plan dated August 23, 2013) to obtain additional salient clinical and diagnostic information related to major hemorrhagic events.

2. Submission of Post-marketing 15-day Alert Reports for all initial and follow-up reports of serious hemorrhagic adverse events from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the

Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) – Haemorrhages.

3. Submission of interval and cumulative analyses, as well as line listing for all major hemorrhagic events (utilizing the SMQ Haemorrhages) from clinical trials and all postmarketing sources, including consumer reports, solicited reports, and foreign reports.

4. The interval and cumulative analyses should assess potential risk factors for cumulative major hemorrhagic events identified from both clinical trials and all postmarketing sources, and an overall assessment about these events in patients treated with Imbruvica® (ibrutinib) Capsules. In the overall assessment, discuss whether the data warrants further detailed assessment, labeling changes and/or other communication about these adverse events.

Continue the study for a period of four years from the date of final protocol submission as noted below. Prior to starting the study, submit for FDA review, a protocol describing how you will conduct the study and report results, according to the timeline below.

The timetable you submitted on November 13, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 03/2014

Final Protocol Submission: 06/2014

#1 Interim Report Submission 12/2014

#2 Interim Report Submission 06/2015

#3 Interim Report Submission 12/2015

#4 Interim Report Submission 06/2016

#5 Interim Report Submission 12/2016

#6 Interim Report Submission 06/2017

#7 Interim Report Submission 12/2017

Study Completion: 06/2018

Final Report Submission: 11/2018

2 RECOMMENDATION

DPV II recommends applying the Imbruvica (ibrutinib) PMR 2060-4, approved under the mantle cell lymphoma (MCL) indication, to the proposed indication of CLL.

3 REFERENCES

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

² Imbruvica (ibrutinib) Pazdur R. Approval Letter. DHHS, dated November 13, 2013. Accessed January 28, 2014 at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

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/s/

TRACY M SALAAM
01/31/2014

SCOTT E PROESTEL
01/31/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 22, 2014

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)
Robert Kane, MD
Deputy Director for Safety
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Division of Medical Policy Programs (DMPP)
Nisha Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): IMBRUVICA (ibrutinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 205552

Applicant: Pharmacyclics, Inc.

1 INTRODUCTION

On June 28, 2013, Pharmacyclics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 205552 for IMBRUVICA (ibrutinib) capsules, with the proposed indication for the treatment of patients with:

- mantle cell lymphoma (MCL) who have received at least one prior therapy
- chronic lymphocytic leukemia (CLL) who have received at least one prior therapy

On October 11, 2013, this NDA was administratively separated with the MCL indication identified as Original #1 and the CLL indication identified as Original #2. On November 13, 2013, IMBRUVICA (ibrutinib) capsules was approved with the indication for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

On January 10, 2014, DMPP and OPDP were consulted to review the PPI for the IMBRUVICA (ibrutinib) Original # 2 indication for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Hematology Products (DHP) on January 10, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IMBRUVICA (ibrutinib) capsules.

2 MATERIAL REVIEWED

- Draft IMBRUVICA (ibrutinib) PPI received on January 9, 2014, and received by DMPP and OPDP on January 16, 2014.
- Draft IMBRUVICA (ibrutinib) Prescribing Information (PI) received on January 9, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 16, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
01/22/2014

NISHA PATEL
01/22/2014

BARBARA A FULLER
01/22/2014

LASHAWN M GRIFFITHS
01/22/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: January 17, 2014

To: Diane Hanner, Senior Program Management Officer
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Karen Rulli, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for
Imbruvica™ (ibrutinib) capsules, for oral use
NDA 205552/Original-2

In response to your consult dated January 10, 2014, we have reviewed the draft Package Insert (PI) for Imbruvica™ (ibrutinib) capsules, for oral use (Imbruvica) that includes changes for Original-2, and offer the following comments. OPDP has made these comments using the version updated by the FDA on 1/16/14.

Section	Statement from draft	Comment
Highlights, Adverse Reactions 6 Adverse Reactions	<p>The most common adverse reactions ($\geq 20\%$) in patients with CLL were thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, pyrexia, constipation, peripheral edema, arthralgia, nausea, stomatitis, sinusitis, and dizziness. (emphasis added)</p> <p>The most commonly occurring adverse reactions ($\geq 20\%$) were thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, pyrexia, constipation, peripheral edema, arthralgia, nausea, stomatitis, sinusitis, and dizziness (See Tables 3 and 4). (emphasis added)</p>	<p>According to Table 3 from the Adverse Reactions section of the full PI, upper respiratory tract infection was reported in 8% of patients. We recommend revising the list of the most commonly occurring adverse reactions in the Highlights, Adverse Reactions and full PI, Adverse Reactions sections to ensure consistency with Table 3 from the full PI.</p>
14 Clinical Studies	(b) (4)	Should the name of the criteria used to

Section	Statement from draft	Comment
	(b) (4)	evaluate tumor response be included in section 14.2 of the full PI?

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/s/

NISHA PATEL
01/17/2014

**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 (PV) Plan

Date: January 10, 2014

Reviewer: Katherine Coyle, PharmD, BCOP
Division of Pharmacovigilance II

Team Leader: Tracy Salaam, PharmD
Division of Pharmacovigilance II

Division Director: Scott Proestel, MD
Division of Pharmacovigilance II

Product Name: Imbruvica (ibrutinib)

Application Type/Number: NDA 205552

Applicant/Sponsor: Pharmacyclics

NDA/BLA Approval Date: November 13, 2013

OSE RCM #: 2013-1058

1 INTRODUCTION

The Pharmacovigilance (PV) Plan documents how the Division of Pharmacovigilance (DPV) II will monitor important identified risks, potential risks, and missing safety information for new drugs or biologics in the postmarketing setting. The PV Plan provides a prospective roadmap for OSE pharmacovigilance activities during the product life cycle. The overall safety management of a product may involve routine PV, Enhanced Pharmacovigilance (EPV), a Risk Evaluation and Mitigation Strategy (REMS), and/or Postmarketing Requirements or Commitments (PMR/PMC). The primary focus of this PV plan will be safety issues requiring routine PV and/or EPV monitoring of ibrutinib.

Routine pharmacovigilance aims to closely monitor, evaluate and further characterize a particular risk, which may include the following: clinical characteristics of the adverse event(s), types of patients at risk (demographic factors), risk factors, characteristics of exposure (dose, duration, concomitant medications). Routine PV also involves the sponsor's and FDA's continuous monitoring of the postmarketing safety profile of approved products and includes signal detection, case evaluation, labeling updates, and communication with external stakeholders. FDA's available sources for safety data may include adverse event reports in FAERS, Empirica Signal, sponsor's periodic reports, published medical literature, completed or ongoing clinical trials and other data sources where appropriate.

EPV is a process to closely monitor select important adverse events and risks that cannot be adequately addressed by routine pharmacovigilance alone. EPV may involve the following: special reporting requirements for sponsors beyond those specified in the code of federal regulation (CFR), such as expedited reporting of labeled adverse events; use of standardized questionnaires for Adverse Events of Special Interest (AESI) for better data collection; and periodic summaries of AESI.

2 PRODUCT INFORMATION¹

- **Approved Indication:** Ibrutinib is a tyrosine kinase inhibitor indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
- **Approved dosing regimen(s) and formulation(s):** The recommended dose is 560 mg (four 140 mg capsules) orally once daily.
- **Mechanism of Action:** Ibrutinib is a first in class small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a

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

cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

3 SAFETY SUMMARY

Table 1 contains a summary of the Safety Specification and PV plan for ibrutinib. This summary serves as a platform to identify the specific important risks that will be closely monitored in the postmarketing setting.

The safety specification considers known and potential risks – the latter being areas of uncertainty regarding safety. It also specifies the limitations of the pre-approval trial data, including the population at risk, and underscores important safety information that is currently missing or outstanding, but requires heightened surveillance.

The important identified risks, potential risks, and missing safety information were identified from the following sources: Office of New Drugs (OND) Reviews, Clinical Trials, Chemistry and Manufacturing, Pharmacology/Toxicology Studies, Clinical Pharmacology/Pharmacokinetics, and Other Related Products.

Limitation of safety database²:

The safety of ibrutinib was evaluated in 120 patients with relapsed or refractory MCL who received at least one but not more than five prior therapies. Safety data was primarily evaluated from a single- arm Phase 2 that enrolled 111 patients who received treatment with ibrutinib. An additional nine subjects with MCL enrolled in the Phase 1 trial were also included in the safety population.

Although ibrutinib was initially approved for treatment of the MCL population, the safety data in this PV plan also reflects the CLL population that was included in the sponsor's reviews at the time of approval.

² OND Clinical Review of Imbruvica (Ibrutinib) dated October 31, 2013 by Karen McGinn.

Table 1. Summary of important safety concerns and planned pharmacovigilance actions for ibrutinib

Safety Specification					DPV PV Plan	Other Post- marketing activities	Reviewer Comments
Category	Safety Issue	Safety Data Source*	Year Identified	Label Location [†]	PV Actions (Routine or Enhanced)	PMR/ PMC/ REMS	
Important identified risks	Hemorrhage	OND Clinical review [†] p. 55	2013	W/P, AR, PCI	Enhanced	PMR 2060-4 Sponsor: Targeted surveillance with use of guided collection form Additional PV (ongoing clinical studies) • Safety analysis on controlled studies to clarify background incidence • Identify potential risk factors based on ongoing studies • Case series analyses across clinical studies	Major bleeding events occurred in 7 (6.3%) patients (pts) and were comprised of subdural hematomas, GI bleeding and hematuria. The sponsor amended the study protocol to have patients avoid concomitant warfarin, and to withhold ibrutinib pre-and post-operatively. The mechanism for hemorrhage remains unknown. Ibrutinib was approved with a PMR to conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with ibrutinib. The PMR will assess potential risk factors for cumulative major hemorrhagic events (including concomitant anticoagulant/antiplatelet therapy).

Safety Specification					DPV PV Plan	Other Post- marketing activities	Reviewer Comments
Category	Safety Issue	Safety Data Source*	Year Identified	Label Location [†]	PV Actions (Routine or Enhanced)	PMR/ PMC/ REMS	
	Infections	OND Clinical review [†] p. 55 Pharmacyclic Clinical Overview [§] p. 35 Pharmacyclics Pharmacovigilance Plan ^{**} p. 7	2013	D/A, W/P, AR, PCI	Routine	Sponsor: Safety analysis on controlled studies to clarify incidence rate	Fatal and non-fatal infections have occurred including sepsis, bacterial, viral, or fungal infections. ^{**} Per the sponsor - three subjects had fatal AEs associated with infections: pneumonia (possibly related), pneumocystis jiroveci pneumonia (possibly related), and sepsis (not related). [§] Infections accounted for the largest percentage of SAEs. [‡]
	Second Primary Malignancies	OND Clinical review [†] p. 57 Pharmacyclics Pharmacovigilance Plan ^{**} p. 8	2013	W/P, AR, PCI	Routine	Sponsor: Additional PV (ongoing clinical studies) • Safety analysis on controlled studies to clarify background incidence • Collect these events during treatment and follow up phase of the studies	Reports of other malignancies have been observed in subjects who have been treated with ibrutinib (4.2% for MCL integrated safety analysis set and 16.2% for CLL integrated safety analysis set). Most of these events were reported as skin carcinomas such as squamous cell carcinoma (2.5% MCL integrated safety analysis set, 6.8% CLL integrated safety analysis set) and basal cell carcinoma (0.8%, 8.5%). Other events reported in ≤ 2 subjects were lung neoplasm, prostate cancer, bladder cancer, glioma, malignant histiocytosis, metastatic neoplasm, and peripheral T-cell lymphoma. ^{**}
	Renal toxicity	OND Clinical review [†] p. 60	2013	W/P, AR, PCI	Routine		Fatal and serious cases of renal failure have occurred with ibrutinib. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal (ULN) occurred in 67% of pts and from 1.5 to 3 times the ULN in 9% of patients. Renal failure which resulted in death occurred in 1 pt. Renal failure in each case was confounded by dehydration, hypovolemia, and/or disease progression, and 5 patients had pre-existing renal failure. [‡]

Safety Specification					DPV PV Plan	Other Post- marketing activities	Reviewer Comments
Category	Safety Issue	Safety Data Source*	Year Identified	Label Location [†]	PV Actions (Routine or Enhanced)	PMR/ PMC/ REMS	
Important potential risks	Lymphocytosis/ Leukostasis	OND Clinical review [†] p. 56 Pharmacocyclics Pharmacovigila nce Plan ^{**} p. 7	2013	Lymphocytosis – labeled Leukostasis – unlabeled	Routine	<p>Sponsor: Leukostasis</p> <ul style="list-style-type: none"> Targeted surveillance with use of guided collection form <p>In ongoing clinical studies:</p> <ul style="list-style-type: none"> Identify potential risk factors based on ongoing studies (eg, white blood cells) Case series analyses across clinical studies 	<p>Upon initiation of ibrutinib treatment, a transient phase of increase in lymphocyte counts (ie, >50% increase from baseline and above absolute count 5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (75% CLL integrated safety analysis set) with relapsed/refractory CLL/SLL treated with single-agent ibrutinib. The effect has also been observed in some subjects (33% MCL integrated safety analysis set) with relapsed/refractory MCL treated with single-agent ibrutinib.</p> <p>Patients who develop <i>lymphocytosis</i> greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.</p> <p><i>Lymphocytosis</i> in patients typically occurs during the first few weeks (median time 1.1 weeks) of ibrutinib therapy and typically resolves within a median of 8-18.7 weeks while on treatment. A large increase in the number of circulating lymphocytes (eg, >400,000/mcL) may increase the risk of <i>leukostasis</i>. There were isolated cases of <i>leukostasis</i> reported in patients treated with ibrutinib.^{**}</p> <p><i>Leukostasis</i> occurred in five pts taking ibrutinib in clinical trials. The cases were confounded by disease progression and it was unclear if there is a safety signal related to ibrutinib. Because <i>leukostasis</i> is a pathologic diagnosis in which white cell plugs are seen in the microvasculature, and there were no pathologic specimens analyzed during the trial, the diagnoses were established empirically based on neurologic symptoms.[‡]</p>

Safety Specification					DPV PV Plan	Other Post- marketing activities	Reviewer Comments
Category	Safety Issue	Safety Data Source*	Year Identified	Label Location [†]	PV Actions (Routine or Enhanced)	PMR/ PMC/ REMS	
	Hypersensitivity	Pharmacyclics Pharmacovigilance Plan** p. 8	2013	Unlabeled	Routine	Sponsor: Targeted surveillance with use of guided collection form Additional PV (ongoing clinical studies) • Identify potential risk factors based on ongoing studies • Case series analyses across clinical studies	In non-randomized clinical trials, hypersensitivity-like adverse event terms such as urticaria and periorbital edema were observed in subjects treated with ibrutinib. These were primarily reported as non-serious and mild in severity (except for one grade 3 event of urticaria in Study PCYC-1102-CA). No severe allergic reactions such as anaphylaxis have been observed to date.**
Important missing information^{††}	QT prolongation	OND Clinical review [†] p. 64		Unlabeled	Routine	PMR 2060-7	The sponsor did not routinely collect ECGs at the initiation of therapy in their QT analysis. The OND Summary Review states QT-IRT recommends a thorough QT study be submitted as a post-marketing requirement.
	Non-white population	Pharmacyclics Pharmacovigilance Plan** p. 9	2013	Unlabeled	Routine	Sponsor: Ongoing clinical studies: • Analysis by race in ongoing studies • Clinical studies in Japan and China	Most subjects were white in clinical studies of MCL and CLL/SLL (92% MCL integrated safety analysis set and 95% CLL integrated safety analysis set); therefore, limited information is available for non-white subjects.**

Safety Specification					DPV PV Plan	Other Post- marketing activities	Reviewer Comments
Category	Safety Issue	Safety Data Source*	Year Identified	Label Location [†]	PV Actions (Routine or Enhanced)	PMR/ PMC/ REMS	
	1 Severe cardiac disease 2 Severe renal disease 3 Hepatic impairment 4 Long exposure (>2 yrs)	Pharmacyclics Pharmacovigila nce Plan** p. 9	2013	Unlabeled	Routine	PMR 2060-5 (Hepatic impairment) Sponsor: Additional PV (ongoing long- term treatment and follow-up clinical studies) • Extension roll-over study (PCYC-1103- CA to collect grade 3/4/5 adverse events)	No formal clinical studies have been conducted in these patients

* Safety data source abbreviations: CP = Clinical Pharmacology/Pharmacokinetics, CMC = Chemistry, Manufacturing and Controls, FPME = Foreign Post-Marketing Experience, MOA = mechanism of action, P/T = Pharmacology/Toxicology Studies, RCT= randomized clinical trial

[†] Label Location Definitions: BW = Boxed Warning, CI = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, D/A= Dosage and Administration, SP= Use in Specific Populations, CP = Clinical Pharmacology, PCI = Patient Counseling Information, MG = Medication Guide

[‡] OND Clinical Review of Imbruvica (Ibrutinib) dated October 31, 2013 by Karen McGinn.

[§] Clinical Overview, Ibrutinib, by Pharmacyclics, Sunnyvale, CA dated June 13, 2013

^{**} Pharmacovigilance Plan, Ibrutinib by Pharmacyclics, Inc., Sunnyvale, CA dated August 23, 2013.

^{††} Important missing information may include safety concerns such as special populations potentially at risk (e.g., populations not studied or studied in a limited degree in the pre-approval phase), potential drug interactions, or non-clinical safety findings that have not been adequately addressed by clinical data. This list is not exhaustive, but focuses on the most important and relevant missing information given the indication for use, known pharmacologic actions of the product, product formulation, and anticipated patient population.

4 SUMMARY OF PROPOSED PHARMACOVIGILANCE ACTIVITIES

As indicated in Table 1, routine PV is proposed for the following *important identified risks* of infections, second primary malignancies, renal toxicity and, *important potential risks* of lymphocytosis/leukostasis and hypersensitivity and *important missing information* about QT prolongation, non-white population, severe cardiac disease, severe renal disease, hepatic impairment and long exposure (>2 years) for ibrutinib.

Enhanced PV was agreed to in PMR 2060-4 in order to characterize the risk of hemorrhage in patients treated with ibrutinib. The EPV study will include:

1. Targeted and expedited surveillance with a guided collection form to obtain additional salient clinical and diagnostic information related to major hemorrhagic events.
2. Submission of Post-marketing 15-day Alert Reports for all initial and follow-up reports of serious hemorrhagic adverse events from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) – Haemorrhages.
3. Submission of interval and cumulative analyses, as well as a line listing for all major hemorrhagic events (utilizing the SMQ Haemorrhages) from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports.
4. The interval and cumulative analyses should assess potential risk factors for cumulative major hemorrhagic events identified from both clinical trials and all postmarketing sources, and an overall assessment about these events in patients treated with ibrutinib. In the overall assessment, discuss whether the data warrants further detailed assessment, labeling changes and/or other communication about these adverse events.

The sponsor will continue the study for a period of four years from the date of final protocol submission. Prior to starting the study, the sponsor will submit for FDA review, a protocol describing how they will conduct the study and report results.

5 POSTMARKETING REQUIREMENTS

1) PEDIATRIC ASSESSMENTS:

Because this drug product for this indication has an orphan drug designation, it is exempt from this requirement.

2) POSTMARKETING REQUIREMENTS (PMR):

At the time of approval, the following PMRs were required:

- 2060-1

Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial PCYC -1104- CA with a minimum follow-up of 24 months for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each patient. In addition, submit detailed assessment information regarding all sites of extranodal disease at baseline and follow-up, including assessments for response and progression. Summarize extranodal disease characteristics at baseline and at time of progression.

- Final Reporting Submission: March 2015
- 2060-2
Complete and submit the final results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. Enrollment of approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators. Overall survival is a key secondary endpoint.
 - Final Reporting Submission: March 2019
- 2060-3
Determine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).
 - Final Report Submission: December 2016
- 2060-4
Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with ibrutinib. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs.
 - Draft Protocol Submission: 03/2014
 - Final Protocol Submission: 06/2014
 - #1 Interim Report Submission 12/2014
 - #2 Interim Report Submission 06/2015
 - #3 Interim Report Submission 12/2015
 - #4 Interim Report Submission 06/2016
 - #5 Interim Report Submission 12/2016
 - #6 Interim Report Submission 06/2017
 - #7 Interim Report Submission 12/2017
 - Study Completion: 06/2018
 - Final Report Submission: 11/2018

- 2060-5
Evaluate the effect of hepatic impairment on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1006 entitled, “An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects with Varying Degrees of Hepatic Impairment”.
 - Final Report Submission: December 2014
- 2060-6
Determine effect of a strong CYP3A Inducer on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1010 entitled, “An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects”.
 - Final Report Submission: April 2014
- 2060-7
Determine the effect of ibrutinib on the QT/QTc interval in healthy subjects on one or more therapeutic dose levels. Conduct and submit results of a thorough QT trial to evaluate the effects of ibrutinib on the QT /QTc interval.
 - Final Report Submission: December 2015

3) POSTMARKETING COMMITMENTS (PMC):

At the time of approval, the following PMCs were requested:

- 2060-8
Collect additional dissolution profile data (n=12 at release and n=12 on stability) using USP Apparatus Type 2 (Paddle) at 75 rpm in 3.0% w/v polysorbate 20 (Tween® 20) in 50 mM phosphate buffer pH 6.8 at 37.0°C from at least ten drug product release batches and from the drug product stability-registration/ primary batches through 12 months of storage at the long-term condition. Use the overall dissolution data that were collected from the drug product’s release and stability batches to set the final dissolution acceptance criteria.
 - Final Report Submission: February 2015

4) RISK EVALUATION AND MITIGATION STRATEGY (REMS):

- A REMS is not required for ibrutinib at this time.

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/s/

KATHERINE M COYLE
01/10/2014

TRACY M SALAAM
01/10/2014

SCOTT E PROESTEL
01/10/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 17, 2013

TO: Diane Hanner, M.P.H., M.S.W., Regulatory Project Manager
Nicole Verdun, M.D., Medical Officer
Karen McGinn, M.S.N., C.R.N.P., Clinical Analyst
R. Angelo de Claro, M.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections
NDA#: 205552
APPLICANT: Pharmacyclics, Inc.
DRUG: ibrutinib
NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority (breakthrough therapy)

INDICATION: Treatment of mantle cell lymphoma with at least one prior therapy and
chronic lymphocytic leukemia with at least one prior therapy

CONSULTATION REQUEST DATE: June 13, 2013 (Signed)
INSPECTION SUMMARY GOAL DATE: September 16, 2013 (Original)
September 23, 2013 (DHP Extension)
DIVISION ACTION GOAL DATE: October 31, 2013 (Original)
PDUFA DATE: October 31, 2013

I. BACKGROUND:

Ibrutinib is a selective and irreversible inhibitor of the Bruton tyrosine kinase protein. Ibrutinib blocks activation of B-cells, arresting cell growth and inducing apoptosis in the human B-cell lymphoma cell lines in vitro, and inhibiting tumor growth in vivo in xenograft models.

Both relapsed or refractory mantle cell lymphoma (MCL), and relapsed or refractory chronic lymphocytic leukemia (CLL) are serious and life-threatening illnesses with approximate median overall survival of two years and five years, respectively. Breakthrough therapy designation is granted by the FDA for therapies such as ibrutinib, where there is preliminary clinical evidence of substantial improvement over existing therapies, for conditions that are serious and life-threatening. Given the high level of activity of ibrutinib in the above hematologic malignancy populations, ibrutinib, if approved, may transform the pharmacological management of patients with CLL or MCL.

The sixth version of the investigational brochure lists diarrhea (40.4%), fatigue (32.1%), and nausea (24.0%) as the most commonly reported treatment-emergent adverse events in studies of ibrutinib administered as monotherapy to 312 subjects. The NCI Common Terminology Criteria for Adverse Events with a severity of Grade 3 and 4 were uncommon, were primarily hematologic in nature, and include anemia, neutropenia, and thrombocytopenia. Serious AEs in the monotherapy studies were commensurate with the disease or its complications, the most common being pneumonia (4.5%) and febrile neutropenia (3.2%).

Two clinical studies were submitted in support of the sponsor's NDA. The CDER review division selected two clinical investigator sites for inspection for each of two studies, Protocols PCYC-1104-CA and PCYC-1102-CA, principally based on the highest number of enrolled patients, highest efficacy treatment responders, and/or highest reported serious adverse events (SAEs).

Study Protocol PCYC-1104-CA

Study PCYC-1104-CA was a Phase 2, open-label, nonrandomized, multicenter, monotherapy study in subjects with histologically-documented mantle cell lymphoma who had relapsed after one or more but not greater than five prior treatment regimens. All subjects meeting eligibility criteria received ibrutinib (PCI-32765) capsules at a dosage of 560 mg once daily for a 28-day cycle until disease progression, unacceptable toxicity, or enrollment in a long-term extension study. The study had two treatment groups in parallel, which were stratified based on prior bortezomib exposure. Efficacy evaluation for overall response and duration of response was performed by the investigator. Overall response was defined as a subject achieving either a partial response or complete response according to the revised International Working Group Criteria for Non-Hodgkins Lymphoma. In addition, the efficacy profile of single agent ibrutinib therapy was confirmed by independent response assessment for the bortezomib-treated cohort.

Study Protocol PCYC-1102-CA

Study PCYC-1102-CA was a Phase 1b/Phase 2, open-label, nonrandomized, multicenter study in subjects with treatment-naïve chronic lymphocytic lymphoma or small lymphocytic lymphoma, relapsed/refractory chronic lymphoma, or high-risk relapsed/refractory chronic lymphocytic lymphoma or small lymphocytic lymphoma. The primary objective was to determine the safety of two fixed dose daily regimens of ibrutinib (PCI-32765) capsules in subjects with chronic lymphocytic lymphoma or small lymphocytic lymphoma. Treatment with ibrutinib was continued until disease progression, withdrawal of consent, or an unacceptable drug-related toxicity occurred. The ibrutinib treatment cohorts consisted of the following: (1) subjects with relapsed/refractory disease on 420 mg/day, (2) treatment-naïve subjects 65 years or older on 420 mg/day, (3) subjects with relapsed/refractory disease on 840 mg/day, (4) subjects with high-risk relapsed/refractory disease on 420 mg/day, (5) treatment-naïve subjects 65 years or older on 840 mg/day, and (6) subjects with relapsed/refractory disease (food-effect cohort) on 420 mg/day. The primary study endpoint was the frequency and severity of adverse events.

II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Kristi A. Blum, M.D. Columbus, OH	Protocol PCYC-1104-CA Site #217 N=14 Protocol PCYC-1102-CA Site #217 N=53	July 22-26, 2013	Pending Preliminary: NAI
Michael L. Wang, M.D. Houston, TX	Protocol PCYC-1104-CA Site #32 N=31	July 23-26, 2013	NAI
Susan M. O'Brien, M.D. Houston, TX	Protocol PCYC-1102-CA Site #32 N=42	July 18-26, 2013	Pending Preliminary: NAI
Pharmacylics, Inc. Sunnyvale, CA	Sponsor	August 23-September 11, 2013	Pending Preliminary: VAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed out, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. **Kristi A. Blum, / Protocol PCYC-1104-CA/Site #217 and Protocol PCYC-1102-CA/Site #217**
Columbus, OH

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from July 22 to 26, 2013.

For Study 1102, a total of 65 subjects were screened and 53 subjects were enrolled. Forty-five subjects completed the study. An audit of 20 subjects' records was conducted.

For Study 1104, a total of 17 subjects were screened and 14 subjects were enrolled. Three subjects are in the long-term follow-up study. An audit of 14 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoints for Study 1102 and Study 1104, respectively, were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. **Michael L. Wang, M.D./Protocol PCYC-1104-CA/Site #32**
Upland, CA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from July 23 to July 26, 2013. A total of 32 subjects were screened and 31 subjects were enrolled. Thirteen subjects were on-going participants at the completion of the study.

An audit of the enrolled subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoints were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable for this specific indication.

**3. Susan M. O'Brien, /Protocol PCYC-1102-CA/Site #32
Houston, TX**

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from July 18 to July 26, 2013. A total of 45 subjects were screened and 42 subjects were enrolled. Thirty subjects were on-going participants at the completion of the study.

An audit of 16 screened subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

4. Pharmacyclics, Inc.

Sunnyvale, CA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from August 23 to September 11, 2013.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

The Sponsor maintained adequate oversight of the clinical trials, Protocols PCYC-1102-CA and PCYC-1104-CA. Clinical site monitoring was considered adequate. Appropriate steps were taken by the Sponsor to bring noncompliant sites into compliance. There was no evidence of under-reporting of adverse events, serious adverse events, or unexpected adverse events in any of the three clinical investigator sites inspected. All protocol deviations appeared to be adequately reported and addressed at the three clinical investigator sites.

In general, the Sponsor site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the Sponsor inspection for not monitoring the study properly.

Specifically, financial disclosure forms were signed by individuals other than the sub-investigators listed on the financial disclosure forms for Protocol PCYCY-1102-CA. The Sponsor monitors did not detect different signatures on different dates during their review of the regulatory source documents. The Sponsor did not document or address the different signatures on the financial disclosure forms in the Monitoring Reports. For example,

1. Sub-investigator, (b) (6) at Site # (b) (6) signed a financial disclosure form on 11/17/2011 and 2/27/2013. The signature on the 2/27/2013 financial disclosure form appeared to differ significantly from the signature on the 11/17/2011 form. During the inspection, the Sponsor provided a Memo from Site # (b) (6) stating that (b) (6) did not sign the 11/17/2011 financial disclosure form and that the document was signed by another individual.
2. Sub-investigator, (b) (6) at Site # (b) (6) signed a financial disclosure form on 10/04/2011 and 2/12/2013. The signature on the 2/12/2013 financial disclosure form appeared to differ significantly from the signature on the 10/04/2011 form. During the inspection, the Sponsor provided a Memo from Site # (b) (6) stating that (b) (6) did not sign the 10/04/2011 financial disclosure form and that the document was signed by another physician.

Additionally, during the close out meeting of the inspection with the Sponsor, ORA staff noted that for Protocol (b) (6), the Sponsor did not obtain sufficient and accurate financial information from the site investigator to allow complete and accurate certification or disclosure statements. For example,

1. Sub-investigators (b) (6) at Site (b) (6) were listed on the 6/24/2013 Form FDA 1572 but (b) (6) never signed a financial disclosure form.
2. Sub-investigators (b) (6) at Site (b) (6) were added to the Form FDA 1572 on 7/15/2013, and did not sign financial disclosure forms until the period ranging from 8/28/2013 to 9/3/2013.

The regulatory deficiencies cited above were discussed with the DHP Clinical Team, who did not consider these observations critical.

c. Assessment of data integrity:

Notwithstanding the above minor regulatory deficiencies, the study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this NDA, two U.S. clinical investigator sites for Protocol PCYC-1102-CA (Susan O'Brien, M.D. and Kristi Blum, M.D.) and two U.S. clinical investigators site for Protocol PCYC-1102-CA (Michael Wang, M.D. and Kristi Blum, M.D.) were inspected in support of this application. The Sponsor (Pharmacyclics, Inc.) was also audited.

No deficiencies were observed for the clinical study sites. The final regulatory classification for Dr. Wang's site is NAI (No Action Indicated). The preliminary classification for the Dr. Blum and Dr. O'Brien sites is NAI.

Regulatory deficiencies were observed for the Sponsor audit. The preliminary regulatory classification is VAI (Voluntary Action Indicated).

The study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above, where applicable, for the clinical investigator or sponsor audits are based on the preliminary communications from the ORA field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final Establishment Inspection Report (EIR).

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
09/17/2013

JANICE K POHLMAN
09/17/2013

KASSA AYALEW
09/17/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205552 BLA#	NDA Supplement #:S- N/A BLA Supplement #	Efficacy Supplement Type SE- N/A
Proprietary Name: IMBRUVICA- (7-12-13 request for new proprietary Name Review was received.)		
Established/Proper Name: Ibrutinib (PCI-32765) Dosage Form: Oral Capsule Strengths: 140 mg		
Applicant: Pharmacyclics, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: June 28, 2013 Date of Receipt: June 28, 2013 Date clock started after UN:		
PDUFA Goal Date: February 28, 2014 (8 months)	Action Goal Date (if different): October 31, 2013	
Filing Date: August 27, 2013	Date of Filing Meeting: August 7, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indications: * Mantle Cell lymphoma Indication *Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) indications		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

	products <input type="checkbox"/> Other (drug/device/biological product)
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<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 102688

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> If yes, explain in comment column.		X		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	N/A not on AIP list
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Please note that this application has an Orphan Designation

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="201 1488 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Not required since this is an orphan designated indication.
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			Sent 6-5-13
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Sent 6-5-13
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Sent 6-5-13
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				N/A- this is not OTC
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?			X	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?			X	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			QT- sent 7-15-13 DSI- sent 6-13-13

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): EOP2- December 5, 2011-CLL & SLL EOP2-March 7, 2012, MCL <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 9, 2013 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): SPA –October 12, 2013- CLL & SLL <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 24, 2013

NDA #: 205552

PROPRIETARY NAME: IMBRUVICA- Submitted but not approved

ESTABLISHED/PROPER NAME: PCI-32765 (ibrutinib)

DOSAGE FORM/STRENGTH: Oral Capsule, 140 mg

APPLICANT: Pharmacyclics, Inc.

PROPOSED INDICATIONS:

- Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)
- Mantle Cell lymphoma

BACKGROUND: The ibrutinib application was granted as a rolling submission. The applicant submitted part 1 which contained nonclinical information on April 25, 2013. The part 2 submission which contained the clinical study reports was received on May 31, 2013. The final part 3 submission which included the CMC modules was received on June 28, 2013. Additional background regarding the specific indications is delineated below:

- PCI-32765 (ibrutinib) which was designated Fast Track on October 29, 2012, for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have relapsed or have refractory disease and have previously received at least one prior therapy.
- Additionally, PCI-32765 (ibrutinib) which was designated for Fast Track on December 18, 2012, for the treatment of patients with Mantle Cell lymphoma (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diane Hanner	Y
	CPMS/TL: (acting)	Theresa Carioti	N
Cross-Discipline Team Leader (CDTL)	R. Angelo de Claro		Y
Clinical	Reviewer:	Karen McGinn & Nicole Verdun	Y
	TL:	R. Angelo de Claro	Y

Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Elimika Pfuma & Marathe Anshu	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Yun Wang	Y
	TL:	Nie, Lei	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shwn-Luan Lee	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	(Robert) Donghao Lu (Xiaohong) Xiao Chen	Y
	TL:	Janice Brown & Jean Tang	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:		

	TL:	Janice Pohlman	N
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	N
	TL:	Cynthia LaCivita	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	Sharon Mills		Y
Other attendees	Ann Farrell; Edvardas Kaminskas; Robert Kane; Kristopher Kolibab; Laura Wall; Peter Waldron		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The clinical study design was acceptable.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p>	<input type="checkbox"/> Not Applicable

<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	<p>None- The late CMC submission was agreed upon during the Pre-NDA meeting was included in Module 3 of the rolling submission.</p>

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): August 14, 2013</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).

<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter-
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIANE C HANNER
08/21/2013

THERESA A CARIOTI
08/23/2013

**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**

Label, Labeling and Packaging Review

Date: August 1, 2013

Reviewer: Kevin Wright, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Ibrutinib Capsules
140 mg

Application Type/Number: NDA 205552

Applicant/sponsor: Pharmacyclics, Inc.

OSE RCM #: 2013-1059

*** This document contains proprietary and confidential information that should not be released to the public.***

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3	CONCLUSIONS.....	2
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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Ibrutinib NDA 205552 for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 26, 2013 submission.

- Active Ingredient: Ibrutinib
- Indication of Use: is a Bruton tyrosine kinase inhibitor indicated for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, and small lymphocytic lymphoma in patients who have received at least one prior therapy.
- Route of Administration: Oral
- Dosage Form: Capsule
- Strength: 140 mg
- Dose and Frequency:
 - Mantel cell lymphoma: 560 mg orally daily
 - Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: 420 mg orally daily
 - Dose Adjustment

Toxicity Occurrence	Mantle cell lymphoma Modification after Recovery	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma after Recovery
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart 140 mg daily
Fourth	Discontinue therapy	

- How Supplied: 90 and 120 count bottles
- Storage: store between 20° to 25°C(68° to 77°F); excursions permitted between 15° to 30° C (59° to 86°F)
- Container and Closure System: High density polyethylene (HDPE) bottles of 90 and 120 capsules

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 28, 2013 (Appendices A and B)
- Carton Labeling submitted June 28, 2013 (Appendices C and D)
- Insert Labeling submitted July 26, 2013 (no image)

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA.

I. Comments to the Division

A. General Comments

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.² As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
 - i. Revise the "≥" symbol appearing in Section 2.4 (Dose Modifications) to read "greater than or equal to Grade 3 non-hematological".
2. We note the use of the abbreviations (e.g. BTK, MCL, CLL, (b) (4)) in the dosage and administration sections in the highlights of prescribing and full prescribing information. We recommend the Applicant, provide the intended meaning of those abbreviations prior to their use to prevent misinterpretation and confusion (e.g. Bruton's tyrosine kinase, mantle cell

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

lymphoma, chronic cell lymphoma, (b) (4) etc)
prior to the use of these abbreviations.

B. Highlights of Prescribing Information

1. In the Dosage and Administration section, we recommend using bullet points to delineate each indication followed by the recommended dose and insertion of a blank line between the two bullets to further help delineate the dosing regimens.

II. Comments to the Applicant

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Labels

1. Ensure the proprietary name on the container label appears in title case (e.g. Tradename) to optimize the readability of the proprietary name.
2. Ensure the established name appears at ½ the font size as of the proprietary name taking into account all pertinent factors, including font size, typography, layout, contrast, coloring and other printing features.
3. Delete the color block appearing on the statement of net quantity because this net quantity competes with the product strength for prominence. Thus, the net quantity may be interpreted as the strength of the product. Additionally, relocate the net quantity statement to the lower third of the principle display panel (PDP) away from the statement of strength.
4. Add the safety statement, “Swallow capsule whole on empty stomach”, to the principle display panel of the container label.
5. We note (b) (4) are proposed on the label. We recommend deleting (b) (4) portion of the label.
6. Debold the “Rx Only” statement.

B. Carton Labeling

1. Ensure the carton labeling complies with recommendations A1 through A6.
2. Delete the (b) (4) from the two side panels to inform practitioners that the panel is a side panel and not the principle display panel.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN WRIGHT
08/01/2013

YELENA L MASLOV
08/01/2013

SCOTT M DALLAS
08/01/2013