DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552

ACCELERATED APPROVAL

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
9995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your New Drug Application (NDA) dated June 28, 2013, received June 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica® (ibrutinib) Capsules, 140 mg.

We acknowledge receipt of your amendments dated May 6, 2013; May 13, 2013; June 6, 2013; June 20, 2013; July 12, 2013; July 25, 2013 (2); July 26, 2013 (3); July 30, 2013; August 1, 2013; August 2, 2013 (7); August 5, 2013(2); August 6, 2013; August 7, 2013; August 9, 2013; August 12, 2013; August 13, 2013 (3); August 14, 2013 (11); August 15, 2013; August 16, 2013; August 19, 2013; August 20, 2013; August 21, 2013; August 23, 2013; August 26, 2013; August 29, 2013; August 30, 2013; September 4, 2013; September 6, 2013; September 9, 2013 (3) September 11, 2013; September 12, 2013; September 17, 2013 (2); September 18, 2013; September 23, 2013; September 24, 2013; September 25, 2013; October 1, 2013; October 3, 2013(2); October 8, 2013; October 11, 2013; October 16, 2013(3); October 18, 2013; October 23, 2013; October 24, 2013; October 29, 2013(2); October 31, 2013 (3); November 5, 2013; November 12, 2013; November 13, 2013(2).

This new drug application provides for the use of Imbruvica (ibrutinib) Capsules, 140 mg for the treatment of patients with Mantle Cell lymphoma (MCL).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

We note that your November 12, 2013, submission includes final printed labeling (FPL) for your: package insert, patient package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your November 13, 2013, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for Imbruvica (ibrutinib) Capsules, 140 mg was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated November 13, 2013. These requirements, along with required completion dates, are listed below.

PMR 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. Request further documentation as necessary from clinical trial sites in order to summarize the details of the extranodal disease progression.

Final Protocol Submission:	Complete 01/2013
Trial Completion:	09/2014
Final Report Submission:	03/2015

PMR 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 Protocol Submission:	Completed 04/2013
Trial Completion:	12/2018
Final Report Submission:	03/2019

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of inhibition of platelet function or assess a known serious risk of bleeding, including major hemorrhagic events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 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).

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

Draft Protocol Submission:	06/2014
Final Protocol Submission:	12/2014
Study Completion:	06/2016
Final Report Submission:	12/2016

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 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 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

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