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

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of:

- Altered ibrutinib exposures (plasma concentrations) and resultant serious adverse effects of treatment in patients with hepatic impairment, or with concomitant use of CYP3A inducers (e.g. rifampin);
- Ibrutinib-induced Q-T prolongation and the potential for torsade de pointes.

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

PMR 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".

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

Final Protocol Submission:	Completed 11/2012
Trial Completion:	06/2014
Final Report Submission:	12/2014

PMR 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".

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

Final Protocol Submission:	Completed 01/2013
Trial Completion:	Completed 01/2013
Final Report Submission:	04/2014

PMR 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.

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

Draft Protocol Submission:	03/2014
Final Protocol Submission:	06/2014
Trial Completion:	06/2015
Final Report Submission:	12/2015

Submit protocols for our review and concurrence prior to initiating and in time to reach agreement in advance of the final protocol submission date.

Submit the protocol to your IND 102688, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 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.

Submit the final report with the complete dissolution information/data and a proposal for the dissolution acceptance under a supplement to the NDA within 15 months from action date.

Study Completion:	11/2014
Final Report Submission:	02/2015

Submit clinical protocols to your IND 102688 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST- APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

You will be contacted by ERG to schedule the interview following this action on your application; ERG will provide specifics about the interview process at that time. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
11/13/2013