DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552/S-001

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENTS
RELEASE FROM POSTMARKETING REQUIREMENT

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

Dear Ms. Salido:

Please refer to your Supplemental New Drug Application (sNDA) dated April 7, 2014, received April 7, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica (ibrutinib) capsules,140mg.

We acknowledge receipt of your amendments dated December 17, 2013; April 14 and 23, 2014; May 23, 27, 29, and 30, 2014; June 3, 9, and 16, 2014; and July 24, 2014.

This Prior Approval supplemental new drug application proposes the indication: Imbruvica is a kinase inhibitor indicated for the treatment of patients with:
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia with 17p deletion.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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), with the

addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART H FULFILLED

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. As we advised in the accelerated approval letter of February 12, 2014, approval of this supplement fulfills your accelerated approval requirements, listed below, made under 21 CFR 314.510 for the following indication: chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

PMR 2122-1 Complete and submit the results of the ongoing 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 approximately 350 patients is expected. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	Completed
Trial Completion:	01/2014
Final Report Submission:	06/2014

We have reviewed your submission and conclude that the above requirement was fulfilled.

RELEASE OF ACCELERATED APPROVAL POSTMARKETING REQUIREMENT

We refer to the following postmarketing requirement listed in the February 12, 2014 approval letter.

PMR 2122-2 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 at approximately 580 patients is expected. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	Completed
Trial Completion:	07/2016
Final Report Submission:	11/2016

We have determined that you are released from the above requirement because PMR 2122-1 fulfilled the accelerated approval requirement. Therefore, while this trial is not required under Subpart H, we encourage you to complete this trial.

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.

FULFILLMENT OF POSTMARKETING REQUIREMENT UNDER 505(o)

We have received your submission dated December 17, 2013, containing the final report for the following postmarketing requirement listed in the November 13, 2013 approval letter.

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

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements and a postmarketing commitment listed in the November 13, 2013 approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, MD
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

EDVARDAS KAMINSKAS
07/28/2014