DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552/S-007

SUPPLEMENT APPROVAL

Pharmacyclics LLC
Attention: Jill Herendeen, PharmD, RAC
Senior Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Dr. Herendeen:

Please refer to your Supplemental New Drug Application (sNDA) dated September 10, 2015, received September 10, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for IMBRUVICA® (ibrutinib) Capsules, 140 mg.

This "Prior Approval" supplemental new drug application provides for a frontline indication of IMBRUVICA® (ibrutinib) for the treatment of Chronic Lymphocytic Leukemia.

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.

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 the drug product for this indication has 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.

Since IMBRUVICA® (ibrutinib) was approved on February 12, 2014, we have become aware of the possibility of increased risks with long-term use of IMBRUVICA® (ibrutinib) based on the results from clinical trials submitted to the NDA: PCYC-1102-CA, PCYC-1104-CA, PCYC-1118E, PCYC-1112-CA, and PCYC-1115-CA. These include, but are not limited to, hemorrhage, infection, cytopenias, atrial fibrillation, hypertension, and second primary malignancies. We consider this "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 assess signals of serious risks of long-term IMBRUVICA® (ibrutinib) treatment including hemorrhage, infection, cytopenias, atrial fibrillation, hypertension, and second primary malignancies.

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 these serious risks.

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

PMR 3038-1 Conduct a study to characterize the safety of long-term exposure to Imbruvica based on data and pooled analyses from trials of patients with mantle cell lymphoma and chronic lymphocytic leukemia. Submit 3-year, 4-year, and 5-year safety follow-up data and reports for a minimum population of 1000 patients treated with approved ibrutinib dosing regimens. Datasets should include patient-level data on ibrutinib dosing, treatment-emergent adverse events, and treatment-emergent laboratory information. This patient set may include approximately 350 patients who continue receiving long-term ibrutinib therapy after completion of primary analysis of the parent study, where study procedures are then limited to collect a minimum of Grade 3+ adverse events, available treatment emergent laboratory data, adverse events leading to treatment discontinuation and SAEs. Study reports should include analyses of adverse event categories listed in the current Warnings and Precautions section of the prescribing information, adverse events leading to treatment discontinuation, and serious adverse events.

The timetable you submitted on February 19, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2016
Interim 3-year Data and Report Submission:	04/2017
Interim 4-year Data and Report Submission:	04/2018
Final Data and Report Submission:	04/2019

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.

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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf.

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 Elleni Alebachew, Regulatory Project Manager, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
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
03/04/2016