DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210563/Original 2

ACCELERATED APPROVAL

Pharmacyclics LLC
Attention: Usha Ramesh, PhD
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Dr. Ramesh:

Please refer to your New Drug Application (NDA) dated August 31, 2017, received August 31, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica® (ibrutinib) tablets, 140 mg, 280 mg, 420 mg, and 560 mg.

NDA 210563 provides for the use of Imbruvica® for the following indications which, for administrative purposes, we have designated as follows:

- NDA 210563/Original 1 – Treatment of adult patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion, Waldenström's macroglobulinemia (WM), and chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

- NDA 210563/Original 2 – Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, and marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

The subject of this action letter is NDA 210563/Original 2. A separate action letter will be issued for NDA 210563/Original 1.

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.

EXPIRATION DATING PERIOD

We grant a 24-month expiration period for the drug product when stored at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 (package insert and 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

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on February 14, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 210563**." Approval of this submission by FDA is not required before the labeling is used.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing 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 requirement for treatment of patients with mantle cell lymphoma who have received at least one prior therapy, specified in your submission dated February 6, 2018. This requirement, along with required completion dates, is listed below.

PMR 3343-1 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.

Trial Completion:	12/2018
Final Report Submission:	03/2019

We remind you of your postmarketing requirement for treatment of patients with marginal zone lymphoma who require systemic therapy specified in your submission dated February 6, 2018. This requirement, along with required completion dates, is listed below.

PMR 3343-2 Submit the complete final report and data from a randomized, Phase 3 trial, comparing ibrutinib in combination with bendamustine and rituximab or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone versus bendamustine and rituximab or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in subjects with previously treated follicular lymphoma or marginal zone lymphoma. At least 50 enrolled subjects need to have a diagnosis of marginal zone lymphoma. The primary endpoint is progression-free survival in the overall intent-to-treat population.

Trial Completion:	05/2019
Final Report Submission:	08/2019

Under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement 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 trial.

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.

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

REPORTING REQUIREMENTS

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

If you have any questions, please contact Jennifer Lee, Regulatory Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Deputy Division Director (Acting)
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
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/

ROMEO A DE CLARO
02/16/2018