NDA 205552/S-029
NDA 210563/S-004

SUPPLEMENT APPROVAL
FULFILLMENT OF POST MARKETING REQUIREMENT

Pharmacyclics LLC
Attention: Preeti Sarde
Manager, Regulatory Affairs
999 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Sarde:

Please refer to your supplemental new drug applications (sNDAs) dated May 24, 2019, received May 24, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for IMBRUVICA (ibrutinib) capsules and tablets.

These Prior Approval supplemental new drug applications provide for updates to the United States Prescribing Information Adverse Reactions section with long-term safety data from the final report for PMR 3038-01, entitled "*Assessment of Safety Risks with Long-term use of IMBRUVICA® (Ibrutinib): A Post Marketing Requirement*."

APPROVAL & LABELING

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

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), 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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated May 24, 2019, containing the final report for the following postmarketing requirement listed in March 4, 2016 (NDA 205552) approval letter.

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

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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.

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

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our March 4, 2016 (NDA 205552) letter.

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 Prescribing Information 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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf

Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

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, contact Patricia Garvey, Lead Regulatory Project Manager, at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANN T FARRELL
11/21/2019 05:50:07 PM