NDA 205552/S-040
NDA 210563/S-017

SUPPLEMENTS APPROVAL
RELEASE FROM POSTMARKETING REQUIREMENTS

Pharmacyclics LLC
Attention: Xiaoran Xu, MS
Manager, Regulatory Affairs
1000 Gateway Blvd
South San Francisco, CA 94080

Dear Xiaoran Xu:

Please refer to your supplemental new drug applications (sNDAs) dated and received April 6, 2023, for NDA 205552/S-040 and NDA 210563/S-017 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 revisions to the US Prescribing Information to voluntarily remove the following indications, previously approved under accelerated approval:

- treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
- treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy

NDA 210563/S-017 also provides for removal of the 560 mg ibrutinib tablet.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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 and Patient 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 *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 applications, you are exempt from this requirement.

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

RELEASE FROM POSTMARKETING REQUIREMENTS

We have received your submissions dated April 6, 2023, related to the following postmarketing requirements listed in the following approval letters for NDA 205552 ibrutinib capsules and NDA 210563 ibrutinib tablets:

- NDA 205552/Original 1, November 13, 2013

  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

- NDA 205552/S-016, January 18, 2017

  3150-1 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.

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

- NDA 210563/Original 2, February 16, 2018

  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

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

We have reviewed your submissions and have determined that you are released from the above requirements as they are no longer needed because the indications in MCL and MZL have been withdrawn from the label.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our November 13, 2013, January 18, 2017, and February 16, 2018, letters.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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 Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Theresa Carioti, MPH, Chief Project Management Staff at 301-796-2848.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

NICOLE J GORMLEY
05/18/2023 01:08:32 PM