



NDA 205552/S-002

**SUPPLEMENT APPROVAL  
POST MARKETING FULFILLMENT**

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 October 17, 2014, received October 17, 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 October 30; November 3, 7, 20, and 24 (2); December 2, 15, 22, and 23, 2014; and January 7 and 20, 2015.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of patients with Waldenström's macroglobulinemia and fulfillment of the postmarketing requirement trial, PMR 2060-5, "*An Open-Label, Multicenter, Pharmacokinetic, Study of PCI-3265 in Subjects with Varying Degrees of Hepatic Impairment*".

**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 Effectuated" (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).

### **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.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

2867-1      Develop and test the stability of a lower (35 or 70 mg) strength ibrutinib capsule in order to allow dose reductions for patients with moderate hepatic impairment for whom ibrutinib treatment is currently not recommended. The lower strength capsule should be sufficiently distinguishable from the 140 mg capsule.

The timetable you submitted on January 23, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2015
Study Completion:	12/2016
Final Report Submission:	03/2017

Submit clinical protocols to your IND 102688 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment 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 study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **FULFILLMENT OF POSTMARKETING REQUIREMENT UNDER 505(o)**

We have received your submission dated September 30, 2014, containing the final report for the following postmarketing requirement listed in the November 13, 2013 approval letter.

PMR 2060-5 Evaluate the effect of hepatic impairment on ibrutinib pharmacokinetics. Submit the final report for trial PCI -32765CLL1006 entitled, “*An Open-Label, Multicenter, Pharmacokinetic, Study of PCI-3265in Subjects with Varying Degrees of Hepatic Impairment.*”

The timetable you submitted on November 13, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission: Completed 11/2012  
Trial Completion: 06/2014  
Final Report Submission: 12/2014

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}*

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

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANN T FARRELL  
01/29/2015