



NDA 202570/S-014

**SUPPLEMENT APPROVAL/  
FULFILLMENT OF POSTMARKETING COMMITMENT**

PF PRISM C.V.  
c/o Pfizer, Inc.  
Attention: J. Nicole Earnhardt, Ph.D., RAC  
Manager, Worldwide Safety & Regulatory  
10646 Science Center Drive  
San Diego, CA 92121

Dear Dr. Earnhardt:

Please refer to your Supplemental New Drug Application (sNDA) dated November 14, 2014, received November 14, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XALKORI (crizotinib).

We acknowledge receipt of your amendments dated February 13 (2), February 23, March 11, March 20, May 22, June 1, June 19, June 29, July 13, July 29, September 1, September 4, September 9, September 10, September 11, and September 14 (3), 2015.

This Prior Approval supplemental new drug application provides for inclusion of data from Study A8081014 (Study 1) in the Adverse Reactions and Clinical Studies sections, inclusion of updated safety information across multiple clinical studies in the Warnings and Precautions section (5.1, 5.2, 5.3, 5.4), a new Warnings and Precautions subsection entitled Severe Visual Loss (5.5), modifications to Dosage and Administration (2.2), modifications to Warnings and Precautions, Embryofetal Toxicity (5.6) and Use in Specific Populations (8.1, 8.2, 8.3, and 8.4), for compliance with the Pregnancy and Lactation Labeling Rule, removal of information in information in Clinical Pharmacology (12.2) based on updates to this information that is now included in Warnings and Precautions (5.3), and modifications to Patient Counseling (17) and Patient Labeling corresponding to modifications of other sections of product labeling.

**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, text for the 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 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 none of these criteria apply to your application, you are exempt from this requirement.

### **FULFILLMENT OF POSTMARKETING COMMITMENTS**

We have also reviewed the results from study A8081014, submitted on November 14, 2015, to fulfill Postmarketing Commitment (PMC) 2100-2. This PMC was listed in the November 20, 2013 sNDA approval letter, as:

- 2100-2 Clinical trial report and datasets from A8081014: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Pemetrexed/Cisplatin or Pemetrexed/ Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus.

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

We remind you that there are still postmarketing requirements and commitments listed in the August 26, 2011, and November 20, 2013, approval letters that are still open.

**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 XALKORI (crizotinib) was approved on August 26, 2011, we have become aware of cases of severe visual loss from clinical trial data and postmarketing adverse event reports. We consider this information to be “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 the known serious risk of severe visual loss.

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 this serious risk.

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

- 2956-1 Conduct an Enhanced Pharmacovigilance Study to evaluate the risk factors for and outcomes of severe visual loss following exposure to XALKORI (crizotinib). This study will include a mechanism to collect, classify, and analyze data on Grade 4 severe visual loss in patients exposed to crizotinib. The study, at a minimum, will include the following key elements:
- Data collection of retrospective data points (best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT), and other evaluations as appropriate for new onset of severe visual loss) to produce informative, reliable outcome measures.
  - Data analysis utilizing descriptive statistics for summarizing data that will fully capture the outcome of concern.

The timetable you submitted on September 14, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/16
Study Start:	03/16
Interim Report Submission:	10/16
Interim Report Submission:	10/17
Interim Report Submission:	10/18
Interim Report Submission:	10/19
Interim Report Submission:	10/20
Study Completion:	03/21
Final Report Submission:	12/21

Each annual interim and final report should constitute a stand- alone report of cumulative severe visual loss outcomes data.

Submit the protocol(s) to your IND 73544, 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>.

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 information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or 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> ).

## **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 Ingrid Fan, Regulatory Project Manager, at (301) 796-5053.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
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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PATRICIA KEEGAN  
09/14/2015