

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**203469Orig1s000**

***Trade Name:* Iclusig™ 15 mg and 45 mg tablets for oral use**

***Generic Name:* Ponatinib**

***Sponsor:* ARIAD Pharmaceuticals, Inc**

***Approval Date:* December 14, 2012**

***Indications:*** Provides for the use of Iclusig™ (ponatinib), 15 mg and 45 mg tablets for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.

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**APPROVAL LETTER**



NDA 203469

**ACCELERATED APPROVAL**

ARIAD Pharmaceuticals Inc.  
Attention: Andrew P. Slugg  
Director, Regulatory Affairs  
26 Landsdowne Street  
Cambridge, MA 02139

Dear Mr. Slugg:

Please refer to your New Drug Application (NDA) dated July 30, 2012, received September 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Iclusig™ (ponatinib) 15 mg and 45 mg tablets for oral use.

We acknowledge receipt of your amendments dated July 30; August 10, 14, 27 (2), 29; September 11 (2), 14 (2), 18, 19, 24, 25, 26, 27, 28; October 1, 3 (3), 4, 9, 12, 16 (2), 19, 24, 31 (2); November 6 (2), 7 (2), 8, 12, 14 (2), 15, 19 (2), 20, 28; and December 6, 12 (2) and 13, 2012.

This new drug application provides for the use of Iclusig™ (ponatinib), 15 mg and 45 mg tablets for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.

We have completed our review of this application. 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.

Based on the provided stability data, an expiration dating period of 12 months is granted for the drug product when stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

### **WAIVER--HIGHLIGHTS**

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 (Medication Guide). 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 enclosed carton and immediate container labels, 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 – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 203469.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **ADVISORY COMMITTEE**

Your application for ponatinib was not referred to an FDA advisory committee because the clinical study design is similar to previously approved products in the class.

### **ACCELERATED APPROVAL REQUIREMENTS**

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing

studies/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 specified in your submission dated December 12, 2012. These requirements, along with required completion dates, are listed below.

PMR 1984-1 Collect sparse PK from ponatinib treated patients in the ongoing trial AP24534-12-301 to characterize exposure-response for Iclusig™ (ponatinib). The exposure-response analysis should be conducted for both efficacy and safety endpoints. Based on the results of these analyses, a trial to evaluate lower dose or an alternate dosing regimen of ponatinib may be necessary.

Draft Protocol Submission: 02/2013  
Final Protocol Submission: 04/2013  
Trial Completion: 08/2015  
Final Report Submission: 02/2016

PMR 1984-2 Conduct a dedicated drug interaction trial in humans to determine the effect of co-administration of the strong CYP3A4 inducer, rifampin, on the pharmacokinetics of Iclusig™ (ponatinib) in healthy subjects.

Final Protocol Submission: 06/2012  
Trial Completion: 06/2013  
Final Report Submission: 12/2013

PMR1984-3 Conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of Iclusig™ (ponatinib) in healthy subjects.

Final Protocol Submission: 06/2012  
Trial Completion: 06/2013  
Final Report Submission: 12/2013

PMR 1984-4 Longer duration follow-up: Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial AP24534-10-201 with 24 months of minimum follow-up for each patient. If 24 months of follow-up is not possible for certain patients, provide justification for each patient.

Final Protocol Submission: 06/2012  
Trial Completion: 12/2013  
Final Report Submission: 06/2014

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.

## **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.

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 signals of the serious risk of hemorrhage and serious toxicity related to high levels of Iclusig™ (ponatinib) from displacement from protein binding sites in the presence of other protein-bound medications...

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:

PMR 1984-5 Characterize the effect of Iclusig™ (ponatinib) on platelet function by evaluating the effect of Iclusig™ (ponatinib) on platelet aggregation *in vitro*.

The timetable you submitted on December 12, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	02/2013
Trial Completion:	09/2013
Final Report Submission:	12/2013

PMR 1984-6 Evaluate the *in vitro* potential for the displacement of Iclusig™ (ponatinib), at a therapeutic concentration, from its protein binding sites in human plasma following addition of frequently used, highly protein-bound co-medications. Positive findings from this *in vitro* study may require additional trials *in vivo*.

The timetable you submitted on December 12, 2012, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2013
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Final Protocol Submission: 04/2013  
Study Completion: 01/2014  
Final Report Submission: 03/2014

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the serious safety risks of hepatic toxicity, cardiovascular toxicity including arterial and venous thrombosis, arrhythmias, pancreatitis, hemorrhage, myelosuppression, tumor lysis syndrome, fluid retention, compromised wound healing, gastrointestinal perforation, and QT prolongation.

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

PMR 1984-7 Conduct a dedicated hepatic impairment trial, since drug clearance may be reduced with hepatic impairment (i.e., Child-Pugh classes A, B and C) on the pharmacokinetics of ponatinib when compared to healthy subjects.

The timetable you submitted on December 12, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/2012  
Trial Completion: 06/2013  
Final Report Submission: 12/2013

PMR 1984-8 To characterize the safety of Iclusig™ (ponatinib), submit longer safety follow-up data of at least 12 months for all ongoing patients in the randomized controlled trial AP24534-12-301 that adequately isolates the effect of the drug.

The timetable you submitted on December 12, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 04/2013  
Trial Completion: 08/2015  
Final Report Submission: 02/2016

PMR 1984-9 Conduct a QT analysis of patients in trial AP24534-12-301 to assess the QT effects of Iclusig™ (ponatinib).

The timetable you submitted on December 12, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 04/2013  
Trial Completion: 08/2015  
Final Report Submission: 02/2016

Submit the protocol(s) to your IND 078375, 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.

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

PMC 1984-10 Submit an updated method *“Identification, Content Uniformity, Assay and Impurities Method for Ponatinib (AP24534) Tablets, 15mg and 45 mg”* (AM1281) to the application via a Supplement, Changes Being Effected – 30 Days (CBE-30).

The timetable you submitted on December 12, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2013

Submit clinical protocols to your IND 078375 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study 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.”**

## **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).

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

## **POST-ACTION FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Office Director  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling  
Carton and Container 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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RICHARD PAZDUR  
12/14/2012