CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:

NDA 203469/S-007 & S-008

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

Generic Name: Ponatinib

Sponsor: ARIAD Pharmaceuticals

Approval Date: December 20, 2013

S-007 provides for revisions to the labeling.
S-008 provides for the addition of a risk evaluation and mitigation strategy (REMS).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203469/S-007 & S-008

SUPPLEMENT APPROVAL
REMS APPROVAL

ARIAD Pharmaceuticals
Attention: Andrew Slugg, MS, MBA
Senior Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139-4234

Dear Mr. Slugg:

Please refer to your Supplemental New Drug Application (sNDA) (S-007) dated November 27, 2013, received November 27, 2013, 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 November 27; December 3, December 12, and December 18, 2013 (2).

We also refer to your Supplemental New Drug Application (sNDA) (S-008) dated December 5, 2013, received December 6, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Iclusig® (ponatinib) tablets.

We acknowledge receipt of your amendment dated December 17, 2013.

We also refer to our letter dated November 25, 2013, notifying you, under Sections 505(o)(3), 505(o)(4) and 505-1 of the FDCA, of new safety information that we believe should be included in the labeling for Iclusig® (ponatinib) tablets, requiring postmarketing studies and clinical trials and requiring a risk evaluation and mitigation strategy (REMS). The new safety information pertains to the risk of serious adverse reactions of vascular occlusions including loss of vision due to blood clots, and occlusion of mesenteric blood vessels, stroke, myocardial infarction, peripheral vascular disease with ischemic necrosis, and other vascular occlusive events.

Supplemental new drug application S-007 provides for revisions to the labeling for Iclusig® (ponatinib) tablets consistent with our November 25, 2013, Safety Labeling Change Notification Letter.

Supplemental new drug application S-008 provides for the addition of a risk evaluation and mitigation strategy (REMS) for Iclusig® (ponatinib) tablets consistent with our November 25, 2013, letter.

We also acknowledge your initiation of a voluntary suspension of marketing of Iclusig® (ponatinib) on October 31, 2013 in light of postmarketing adverse event reports and follow-up data from clinical trials that indicate an increased frequency of serious vascular occlusive events with Iclusig® (ponatinib) treatment.

As noted in our November 25, 2013 letter, we have determined that revised labeling and a REMS are needed to ensure that the benefits of Iclusig outweigh the risks. Once the REMS is fully operational, your suspension of marketing would no longer be warranted. In order to be fully operational, FDA considers that, at a minimum, the Iclusig REMS website will be active with all required information and functional links.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your December 18, 2013 submission includes final printed labeling (FPL) for your Package Insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), 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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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)

Refer to the FDA letter dated November 25, 2013, in which you were notified that 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 vascular occlusion with the use of Iclusig® (ponatinib).

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 2113-1 Propose and conduct an enhanced pharmacovigilance study of data from clinical trials and all postmarketing sources to assess risk factors for, management of, and consequences of all vascular occlusive events that are serious or require medical evaluation or treatment, occurring while patients are receiving ponatinib or within 30 days of the last drug dose.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2014
Final Protocol Submission:	06/2014
Study Completion:	03/2017

Final Report Submission:	12/2017

PMR 2113-2 Conduct a prospective, observational study to evaluate the incidence of and risk factors for vascular occlusive events when ponatinib is given with or without anticoagulant or antiplatelet agents. Submit a protocol that includes measures to ensure sufficient long-term follow-up to adequately capture late occurring vascular occlusive events and describe measures that minimize loss to follow-up.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2014
Final Protocol Submission:	10/2014
Study Completion:	10/2018
Final Report Submission:	06/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of vascular occlusion with the use of Iclusig® (ponatinib).

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

PMR 2113-3 Provide long-term follow-up of all patients enrolled in the Phase 1 (AP24534-07-101) and Phase 2 (AP24534-10-201) clinical trials. Assess the long-term safety of ponatinib treatment, including the long-term risk of vascular occlusive events. Include narratives for all cases of vascular occlusion. The final report submission should include text and data sets.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission:	03/2017

PMR 2113-4 Submit the final report (using a data cut-off of 30 days following the last dose) for the Phase 3 clinical trial, AP24534-12-301 entitled “Phase 3 Randomized, Open-Label Study of Ponatinib vs Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase” in order to characterize the long-term safety of Iclusig. Include narratives for all cases of vascular occlusion. The final report submission should include text and data sets. Include pharmacokinetic exposure-response and dose-response analyses in final report.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

	Final Report Submission:	03/2014

PMR 2113-5 Prepare and submit an integrated safety data and summary (final report submission) from all three clinical trials cited in PMRs 2113-3 and 2113-4 (Phase 1, Phase 2, and Phase 3). Include narratives for all cases of vascular occlusion.

The timetable you submitted on December 18, 2013, states that you will conduct this trial according to the following schedule:

	Final Report Submission:	04/2014

PMR 2113-6 Conduct a randomized, multi-arm trial to characterize the safety of a range of ponatinib doses. The trial should be of sufficient size and duration to inform safe use of Iclusig in chronic phase CML. The trial should also assess the efficacy of the doses investigated. Include a plan for adequate PK sampling to provide exposure-toxicity and exposure-response data sufficient to identify appropriate dose ranges (or exposure targets) for patients with T315I mutation and for patients who have progressed after at least two TKIs and are considered to have no alternative therapy available.

The timetable you submitted on December 18, 2013, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2014
Final Protocol Submission:	07/2014
Trial Completion:	12/2018
Final Report Submission:	06/2019

Submit the protocols to your IND 078375, with a cross-reference letter to this NDA. Submit all final reports 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. The details of the REMS requirements were outlined in our November 25, 2013 REMS notification letter.

Your proposed REMS, submitted on December 17, 2013, and appended to this letter, is approved.

The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of healthcare providers' understanding of the following:
    a. The indications for Iclusig® (ponatinib) are limited to:
        i. treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
        ii. treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated
    b. The serious risks of vascular occlusion and thromboembolism with Iclusig® (ponatinib) treatment.
    c. The Iclusig® (ponatinib) REMS program and materials

2. Program outreach and communication activities
    a. Distribution of the REMS letters
        i. Total number of recipients included in mass mailing of REMS letters, dates of mailings (United States Postal mail and email).
        ii. Stratify letters sent by: number of letters sent to each prescriber specialty, or professional society, number emailed, or sent via U.S. mail, number undeliverable, and if delivered by email, number of emails opened.
    b. Journal Pieces

i. Date journal pieces appeared in each journal or publication and a copy of the journal piece

c. Professional meetings
   i. Date of professional meeting and materials displayed.
d. Number of unique visits to the Iclusig® (ponatinib) REMS website
e. Number of REMS fact sheets distributed by Ariad representatives during follow-up details/ visits with a healthcare provider.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA 203469 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 203469 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 203469
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 203469
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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.

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 or by fax to 301-847-8444.

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 CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
12/20/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ICLUSIG safely and effectively. See full prescribing information for ICLUSIG.

ICLUSIG® (ponatinib) tablets for oral use
Initial U.S. Approval: 2012

WARNING: VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY
See full prescribing information for complete boxed warning

- **Vascular Occlusion: Arterial and venous thrombosis and occlusions have occurred in at least 27% of Iclusig treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion. (5.1).**
- **Heart Failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure (5.2).**
- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected (2.3, 5.4).**

----------RECENT MAJOR CHANGES----------

Boxed Warning	12/2013
Indications and Usage (1)	12/2013
Dosage and Administration (2.1)	12/2013
Warnings and Precautions (5.1, 5.2, 5.4, 5.6, and 5.7)	12/2013

----------INDICATIONS AND USAGE----------
Iclusig is a kinase inhibitor indicated for the:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated. (1)

These indications are based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

----------DOSAGE AND ADMINISTRATION----------

- 45 mg taken orally once daily with or without food (2.1)
- Modify or interrupt dosing for hematologic and non-hematologic toxicity (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 15 mg and 45 mg (3)

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypertension: Monitor for high blood pressure and manage as clinically indicated (5.4, 6).
- Pancreatitis: Monitor serum lipase monthly; interrupt or discontinue Iclusig (2.3, 5.5, 6).
- Neuropathy: (5.6, 6) Monitor for symptoms of peripheral and cranial neuropathy.
- Ocular Toxicity: Conduct comprehensive eye exams at baseline and periodically during treatment (5.7).
- Hemorrhage: Interrupt Iclusig for serious or severe hemorrhage (5.8, 6).
- Fluid Retention: Monitor patients for fluid retention; interrupt, reduce, or discontinue Iclusig (5 9, 6).
- Cardiac Arrhythmias: Monitor for symptoms of arrhythmias (5.10, 6).
- Myelosuppression: Thrombocytopenia, neutropenia, and anemia may require dose interruption or reduction. Monitor complete blood counts every 2 weeks for 3 months and then monthly and as clinically indicated. Interrupt Iclusig for ANC < 1000/mm^3 or thrombocytopenia < 50,000/ mm^3 (2.2, 5.11, 6).
- Tumor Lysis Syndrome: Ensure adequate hydration and correct elevated uric acid levels prior to initiating therapy with Iclusig (5.12).
- Compromised Wound Healing and Gastrointestinal Perforation: Temporarily interrupt therapy in patients undergoing major surgical procedures (5.13).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of potential risk to a fetus (5.14, 8.1).

----------ADVERSE REACTIONS----------
The most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. Hematologic adverse reactions included thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia (6).

To report SUSPECTED ADVERSE REACTIONS, contact ARIAD Pharmaceuticals, Inc. at 1-855-55-ARIAD or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Strong CYP3A Inhibitors: Reduce Iclusig dose if co-administration cannot be avoided (7.1).

----------USE IN SPECIFIC POPULATIONS----------
The safety and efficacy of Iclusig in patients less than 18 years of age have not been tested (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: [12/2013]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY

Vascular Occlusion:

- **Arterial and venous thrombosis and occlusions have occurred in at least 27% of Iclusig treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events (5.1).**
- **Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion. A benefit-risk consideration should guide a decision to restart Iclusig therapy (5.1).**

Heart Failure:

- **Heart failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure (5.2).**

Hepatotoxicity:

- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected (2.3, 5.3).**

1 INDICATIONS AND USAGE

Iclusig (ponatinib) is a kinase inhibitor indicated for the:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) and T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

These indications are based upon response rate *[see Clinical Studies (14)]*. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The optimal dose of Iclusig has not been identified. In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.

Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for CP CML and AP CML patients who have achieved a major cytogenetic response.

Consider discontinuing Iclusig if response has not occurred by 3 months (90 days).

Iclusig may be taken with or without food. Tablets should be swallowed whole.

2.2 Dose Modifications for Myelosuppression

Suggested dose modifications for neutropenia (ANC* less than 1.0 x 10^9/L) and thrombocytopenia (platelet less than 50 x 10^9/L) that are unrelated to leukemia are summarized in Table 1.

Table 1: Suggested Dose Modifications for Myelosuppression

ANC* < 1 x 10^9/L or platelet < 50 x 10^9/L	First occurrence: • Interrupt Iclusig and resume initial 45 mg dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Second occurrence: • Interrupt Iclusig and resume at 30 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Third occurrence: • Interrupt Iclusig and resume at 15 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L

*ANC = absolute neutrophil count

2.3 Dose Modifications for Non-Hematologic Adverse Reactions

If a serious non-hematologic adverse reaction occurs, modify the dose or interrupt treatment. Do not restart Iclusig in patients with arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options. For serious reactions other than arterial or venous occlusion, do not restart Iclusig until the serious event has resolved or the potential benefit of resuming therapy is judged to outweigh the risk.

Hepatic Toxicity

Recommended modifications for hepatic toxicity are summarized in Table 2.

Table 2: Recommended Dose Modifications for Hepatic Toxicity

Elevation of liver transaminase > 3 x ULN* (Grade 2 or higher)	Occurrence at 45 mg: • Interrupt Iclusig and monitor hepatic function • Resume Iclusig at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN) Occurrence at 30 mg: • Interrupt Iclusig and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: • Discontinue Iclusig
Elevation of AST or ALT ≥ 3 x ULN concurrent with an elevation of bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN	Discontinue Iclusig

*ULN = Upper Limit of Normal for the lab

Pancreatitis and Elevation of Lipase

Recommended modifications for pancreatic adverse reactions are summarized in Table 3.

Table 3: Recommended Dose Modifications for Pancreatitis and Elevation of Lipase

Asymptomatic Grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of Iclusig
Asymptomatic Grade 3 or 4 elevation of lipase (> 2 x ULN*) or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis)	Occurrence at 45 mg: • Interrupt Iclusig and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x ULN) Occurrence at 30 mg: • Interrupt Iclusig and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: • Discontinue Iclusig
Symptomatic Grade 3 pancreatitis	Occurrence at 45 mg: • Interrupt Iclusig and resume at 30 mg after complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1 Occurrence at 30 mg: • Interrupt Iclusig and resume at 15 mg after complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1 Occurrence at 15 mg: • Discontinue Iclusig
Grade 4 pancreatitis	Discontinue Iclusig

*ULN = Upper Limit of Normal for the lab

2.4 Dose Modification for Use With Strong CYP3A Inhibitors

The recommended dose should be reduced to 30 mg once daily when administering Iclusig with strong CYP3A inhibitors *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

15 mg and 45 mg round, white, film-coated tablets.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Vascular Occlusion

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in at least 27% of Iclusig-treated patients from the phase 1 and phase 2 trials. Iclusig can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Iclusig can also cause recurrent or multi-site vascular occlusion.

In the dose-escalation (phase 1) clinical trial, 48% (31/65) of patients with CML or Ph+ ALL developed vascular occlusive events. The median time to onset of the first vascular occlusion event was 5 months. Iclusig can cause fatal and life-threatening vascular occlusion in patients treated at dose levels as low as 15 mg per day.

Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia (see Table 4).

Table 4: Vascular Occlusion Incidence in Iclusig-Treated Patients in Phase 2 Trial According to Risk Categories

	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia	**No history of ischemia, hypertension, diabetes, or hyperlipidemia**
Age: 49 or younger	18% (6/33)	12% (13/112)
Age: 50 to 74 years	33% (50/152)	18% (20/114)
Age: 75 and older	56% (14/25)	46% (6/13)
All age groups	33% (70/210)	16% (39/239)
Total	24% (109/449)	

Arterial Occlusion and Thrombosis

Arterial occlusion and thrombosis occurred in at least 20% (91/449) of Iclusig-treated patients with some patients experiencing events of more than one type. Patients have required revascularization procedures (cerebrovascular, coronary, and peripheral arterial) due to vascular occlusion from Iclusig.

Cardiac vascular occlusion, including fatal and life-threatening myocardial infarction and coronary artery occlusion has occurred in 12% (55/449) of Iclusig-treated patients, Patients have developed heart failure concurrent or subsequent to the myocardial ischemic event.

Cerebrovascular occlusion, including fatal stroke has occurred in 6% (27/449) of Iclusig-treated patients. Iclusig can cause stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery).

Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease have occurred in 8% (36/449) of Iclusig-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations.

Clinicians should consider whether the benefits of Iclusig treatment are expected to exceed the risks of therapy. In patients suspected of developing arterial thrombotic events, interrupt or stop Iclusig. A benefit-risk consideration should guide a decision to restart Iclusig therapy. *[see Dosage and Administration (2.3)]*.

Venous Thromboembolism

Venous thromboembolic events occurred in 5% (23/449) of Iclusig-treated patients, including deep venous thrombosis (8 patients), pulmonary embolism (6 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients). Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism *[see Dosage and Administration (2.3)]*.

5.2 Heart Failure

Fatal and serious heart failure or left ventricular dysfunction occurred in 5% of Iclusig-treated patients (N =22). Eight percent of patients (N= 35) experienced any grade of heart failure or left ventricular dysfunction. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of Iclusig. Consider discontinuation of Iclusig in patients who develop serious heart failure *[see Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Iclusig can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with BP-CML or Ph+ ALL. Severe hepatotoxicity occurred in all disease cohorts.

The incidence of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation was 56% (all grades) and 8% (grade 3 or 4). Iclusig treatment may result in elevation in ALT, AST, or both. ALT or AST elevation was not reversed by the date of last follow-up in 5% of patients.

Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue Iclusig as clinically indicated *[see Dosage and Administration (2.3)]*.

5.4 Hypertension

Treatment-emergent hypertension occurred in 67% of patients (300/449). Eight patients (2%) treated with Iclusig in clinical trials experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath *[see Adverse Reactions (6)]*. In patients with baseline systolic BP<140 mm Hg and baseline diastolic BP<90mm Hg, 78% (220/282) experienced treatment-emergent hypertension; 49% (139/282) developed Stage 1 hypertension (defined as systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) while 29% developed Stage 2 hypertension (defined as systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg. In 131 patients with Stage 1 hypertension at baseline, 61% (80/131) developed Stage 2 hypertension. Monitor and manage blood pressure elevations during Iclusig use and treat hypertension to normalize blood pressure. Interrupt, dose reduce, or stop Iclusig if hypertension is not medically controlled.

5.5 Pancreatitis

Clinical pancreatitis occurred in 6% (28/449) of patients (5% grade 3) treated with Iclusig. Pancreatitis resulted in discontinuation or treatment interruption in 6% of patients (25/449). Twenty-two of the 28 cases of pancreatitis resolved within 2 weeks with dose interruption or reduction. The incidence of treatment-emergent lipase elevation was 41%.

Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Dose interruption or reduction may be required. In cases where lipase elevations are accompanied by abdominal symptoms, interrupt treatment with Iclusig and evaluate patients for pancreatitis *[see Dosage and Administration (2.3)]*. Do not consider restarting Iclusig until patients have complete resolution of symptoms and lipase levels are less than 1.5 x ULN.

5.6 Neuropathy

Peripheral and cranial neuropathy have occurred in Iclusig-treated patients. Overall, 13% (59/449) of Iclusig-treated patients experienced a peripheral neuropathy event of any grade (2%, grade 3/4). In clinical trials, the most common peripheral neuropathies reported were peripheral neuropathy (4%, 18/449), paresthesia (4%, 17/449), hypoesthesia (2%, 11/449), and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 1% (6/449) of Iclusig-treated patients (<1% grade 3/4).

Of the patients who developed neuropathy, 31% (20/65) developed neuropathy during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting Iclusig and evaluate if neuropathy is suspected.

5.7 Ocular Toxicity

Serious ocular toxicities leading to blindness or blurred vision have occurred in Iclusig-treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 3% of Iclusig-treated patients. Conjunctival or corneal irritation, dry eye, or eye pain occurred in 13% of patients. Visual blurring occurred in 6% of the patients. Other ocular toxicities include cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment *[see Adverse Reactions (6)]*.

5.8 Hemorrhage

Serious bleeding events, including fatalities, occurred in 5% (22/449) of patients treated with Iclusig. Hemorrhage occurred in 24% of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Cerebral hemorrhage and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia *[see Warnings and Precautions (5.11)]*. Interrupt Iclusig for serious or severe hemorrhage and evaluate *[see Dosage and Administration (2.3)]*.

5.9 Fluid Retention

Fluid retention events judged as serious occurred in 3% (13/449) of patients treated with Iclusig. One instance of brain edema was fatal. Serious fluid retention events in more than 1 patient included: pericardial effusion (6/449, 1%), pleural effusion (5/449, 1%), and ascites (2/449, <1%).

In total, fluid retention occurred in 23% of the patients. The most common fluid retention events were peripheral edema (16%), pleural effusion (7%), and pericardial effusion (3%).

Monitor patients for fluid retention and manage patients as clinically indicated. Interrupt, reduce, or discontinue Iclusig as clinically indicated *[see Dosage and Administration (2.3)]*.

5.10 Cardiac Arrhythmias

Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 1% (3/449) of Iclusig-treated patients. The cardiac rhythms (1 case each) identified were complete heart block, sick sinus syndrome, and atrial fibrillation with bradycardia and pauses. Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness, or chest pain). Interrupt Iclusig and evaluate.

Supraventricular tachyarrhythmias occurred in 5% (25/449) of Iclusig-treated patients. Atrial fibrillation was the most common supraventricular tachyarrhythmia and occurred in 20 patients. The other supraventricular tachyarrhythmias were atrial flutter (4 patients), supraventricular tachycardia (4 patients), and atrial tachycardia (1 patient). For 13 patients, the event led to hospitalization. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness). Interrupt Iclusig and evaluate.

5.11 Myelosuppression

Severe (grade 3 or 4) myelosuppression occurred in 48% (215/449) of patients treated with Iclusig. The incidence of these events was greater in patients with accelerated phase CML (AP-CML), blast phase CML (BP-CML) and Ph+ ALL than in patients with chronic phase CML (CP-CML). Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated, and adjust the dose as recommended *[see Dosage and Administration (2.2)]*.

5.12 Tumor Lysis Syndrome

Two patients (<1%) treated with Iclusig developed serious tumor lysis syndrome. Both cases occurred in patients with advanced CML. Hyperuricemia occurred in 7% (30/449) of patients; the majority had chronic phase CML (19 patients). Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig.

5.13 Compromised Wound Healing and Gastrointestinal Perforation

No formal studies of the effect of Iclusig on wound healing have been conducted. Based on the mechanism of action *[see Clinical Pharmacology (12.1)]*, Iclusig could compromise wound healing. Serious gastrointestinal perforation (fistula) occurred in one patient 38 days post-cholecystectomy.

Interrupt Iclusig for at least 1 week prior to major surgery. The decision when to resume Iclusig after surgery should be based on clinical judgment of adequate wound healing.

5.14 Embryo-Fetal Toxicity

Iclusig can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Ponatinib caused embryo-fetal toxicity in rats at exposures lower than human exposures at the recommended human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Advise women to avoid pregnancy while taking Iclusig *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Vascular Occlusion *[see Warnings and Precautions (5.1)]*
- Heart Failure *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Pancreatitis *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*
- Neuropathy *[see Warnings and Precautions (5.6)]*
- Ocular Toxicity *[see Warnings and Precautions (5.7)]*
- Hemorrhage *[see Warnings and Precautions (5.8)]*
- Fluid Retention *[see Warnings and Precautions (5.9)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.10)]*
- Myelosuppression *[see Dosage and Administration (2.2) and Warnings and Precautions (5.11)]*

The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. All patients received a starting dose of 45 mg Iclusig once daily. At the time of analysis, the median duration of treatment with Iclusig was 337 days in patients with CP-CML, 362 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ ALL. The median dose intensity was 37 mg or 83% of the expected 45 mg dose. The events of arterial ischemia, cardiac failure, and peripheral neuropathy reported in Tables 5 and 6 below include data from an additional 13 months of follow-up (median duration of treatment CP-CML: 672 days, AP-CML: 590 days, BP-CML: 89 days, Ph+ ALL: 81 days).

Adverse reactions reported in more than 10% of all patients treated with Iclusig in this trial are presented in Table 5. Overall, the most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia.

The rates of treatment-emergent adverse events resulting in discontinuation were 13% in CP-CML, 11% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse events that led to treatment discontinuation were thrombocytopenia (4%) and infections (1%).

Dose modifications (dose delays or dose reductions) due to adverse reactions occurred in 74% of the patients. The most common adverse reactions (≥5%) that led to dose modifications include thrombocytopenia (30%), neutropenia (13%), lipase increased (12%), rash (11%), abdominal pain (11%), pancreatitis (6%), and ALT, AST, or GGT increased (6%).

Table 5: Adverse Reactions Occurring in >10% of Patients, Any Group

	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
System Organ Class	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**
Cardiac or Vascular disorders								
Hypertension (a)	68	39	71	36	65	26	53	31
Arterial ischemia (b)*	20	11	19	9	10	5	3	0
Cardiac Failure (c)*	7	4	6	4	15	8	6	3
Gastrointestinal disorders								
Abdominal pain (d)	49	10	40	8	34	6	44	6
Constipation	37	2	24	2	26	0	47	3
Nausea	23	1	27	0	32	2	22	0
Diarrhea	16	1	26	0	18	3	13	3
Vomiting	13	2	24	0	23	2	22	0
Oral mucositis (e)	10	1	15	1	23	0	9	3
GI hemorrhage (f)	2	<1	8	1	11	5	9	6
Blood and lymphatic system disorders								
Febrile neutropenia	1	<1	4	4	11	11	25	25
Infections and infestations								
Sepsis	1	1	5	5	8	8	22	22
Pneumonia	3	2	11	9	13	11	9	3
Urinary tract infection	7	1	12	1	0	0	9	0
Upper respiratory tract infection	11	1	8	0	11	2	0	0
Nasopharyngitis	9	0	12	0	3	0	3	0
Cellulitis	2	1	4	2	11	3	0	0
Nervous system disorders								
Headache	39	3	28	0	31	3	25	0
Peripheral neuropathy (g)*	16	2	11	1	8	0	6	0
Dizziness	11	0	5	0	5	0	3	0
Respiratory, thoracic, and mediastinal disorders								
Pleural effusion	3	1	11	2	13	0	19	3
Cough	12	0	17	0	18	0	6	0
Dyspnea	11	2	15	2	21	7	6	0
Skin and subcutaneous tissue disorders								
Rash and related conditions	54	5	48	8	39	5	34	6
Dry skin	39	2	27	1	24	2	25	0
Musculoskeletal and connective tissue disorders								
Arthralgia	26	2	31	1	19	0	13	0
Myalgia	22	1	20	0	16	0	6	0
Pain in extremity	17	2	17	0	13	0	9	0
Back pain	15	1	11	2	16	2	13	0
Muscle spasms	12	0	5	0	5	0	13	0
Bone pain	12	<1	12	1	11	3	9	3
General disorders and administration site conditions								
Fatigue or asthenia	39	3	36	6	35	5	31	3
Pyrexia	23	1	31	5	32	3	25	0
Edema, peripheral	13	<1	19	0	13	0	22	0

Table 5: Adverse Reactions Occurring in >10% of Patients, Any Group

	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
Pain	8	<1	7	0	16	3	6	3
Chills	7	0	11	0	13	2	9	0
Metabolism and nutrition disorders								
Decreased appetite	8	<1	12	1	8	0	31	0
Investigations								
Weight decreased	6	<1	7	0	5	0	13	0
Psychiatric disorders								
Insomnia	7	0	12	0	8	0	9	0

Adverse drug reactions, reported using MedDRA and graded using NCI-CTC-AE v 4.0 (NCI Common Terminology Criteria for Adverse Events) for assessment of toxicity.
Treatment-emergent, all causality events
(a) derived from blood pressure (BP) measurement recorded monthly while on trial
(b) includes cardiovascular, cerebrovascular, and peripheral vascular ischemia
(c) includes cardiac failure, cardiac failure congestive, cardiogenic shock, cardiopulmonary failure, ejection fraction decreased, pulmonary edema, right ventricular failure
(d) includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort
(e) includes aphthous stomatitis, lip blister, mouth ulceration, oral mucosal eruption, oral pain, oropharyngeal pain, pharyngeal ulceration, stomatitis, tongue ulceration
(f) includes gastric hemorrhage, gastric ulcer hemorrhage, hemorrhagic gastritis, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, intra-abdominal hemorrhage, melena, rectal hemorrhage, and upper gastrointestinal hemorrhage
(g) includes burning sensation, skin burning sensation, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy
* represents an additional 13 months of follow-up

Table 6: Serious Adverse Reactions (SAR)

	N (%)
Cardiovascular disorders	
Arterial ischemic event*	53 (11.8%)
Cardiovascular	28 (6.2%)
Cerebrovascular	18 (4.0%)
Peripheral vascular	16 (3.6%)
Hemorrhage	22 (4.9%)
CNS hemorrhage	10 (2.2%)
Gastrointestinal hemorrhage	10 (2.2%)
Cardiac failure*	22 (4.9%)
Effusions(a)	13 (2.9%)
Atrial fibrillation	11 (2.4%)
Venous thromboembolism	10 (2.2%)
Hypertension	8 (1.8%)
Gastrointestinal disorders	
Pancreatitis	23 (5.1%)
Abdominal pain	17 (3.8%)
Blood and lymphatic system disorders	
Febrile neutropenia	13 (2.9%)
Thrombocytopenia	13 (2.9%)
Anemia	12 (2.7%)
Infections	
Pneumonia	24 (5.3%)
Sepsis	11 (2.4%)
General	
Pyrexia	14 (3.1%)

(a)includes pericardial effusion, pleural effusion, and ascites
* represents an additional 13 months of follow-up

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML (see Table 7).

Table 7: Incidence of Clinically Relevant Grade 3/4* Hematologic Abnormalities

Laboratory Test	CP-CML (N=270) (%)	AP-CML (N=85) (%)	BP-CML (N=62) (%)	Ph+ ALL (N=32) (%)
Hematology				
Thrombocytopenia (platelet count decreased)	36	47	57	47
Neutropenia (ANC decreased)	24	51	55	63
Leukopenia (WBC decreased)	14	35	53	63
Anemia (Hgb decreased)	9	26	55	34
Lymphopenia	10	26	37	22

ANC=absolute neutrophil count, Hgb=hemoglobin, WBC=white blood cell count
*Reported using NCI-CTC-AE v 4.0

Table 8: Incidence of Clinically Relevant Non-Hematologic Laboratory Abnormalities

Laboratory Test	Safety Population N=449	
	Any Grade* (%)	CTCAE Grade 3/4 (%)
Liver function tests		
ALT increased	53	8
AST increased	41	4
Alkaline phosphatase increased	37	2
Albumin decreased	28	1
Bilirubin increased	19	1
Pancreatic enzymes		
Lipase increased	41	15
Amylase increased	3	<1
Chemistry		
Glucose increased	58	6
Phosphorus decreased	57	8
Calcium decreased	52	1
Sodium decreased	29	5
Glucose decreased	24	0
Potassium decreased	16	2
Potassium increased	15	2
Sodium increased	10	<1
Bicarbonate decreased	11	<1
Creatinine increased	7	<1
Calcium increased	5	0
Triglycerides increased	3	<1

ALT=alanine aminotransferase, AST=aspartate aminotransferase.
*Graded using NCI-CTC-AE v 4.0

7 DRUG INTERACTIONS

Based on *in vitro* studies, ponatinib is a substrate of CYP3A4/5 and to a lesser extent CYP2C8 and CYP2D6. Ponatinib also inhibits the P-glycoprotein (P-gp), ATP-binding cassette G2 (ABCG2) [also known as BCRP], and bile salt export pump (BSEP) transporter systems *in vitro [see Clinical Pharmacology (12.3)]*.

7.1 Drugs That Are Strong Inhibitors of CYP3A Enzymes

In a drug interaction study in healthy volunteers, co-administration of Iclusig with ketoconazole increased plasma ponatinib $AUC_{0\text{-}inf}$ and C_{max} by 78% and 47%, respectively *[see Clinical Pharmacology (12.3)]*. When administering Iclusig with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole), the recommended starting dose should be reduced *[see Dosage and Administration (2.1)]*. Patients taking concomitant strong inhibitors may be at increased risk for adverse reactions *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs That Are Strong Inducers of CYP3A Enzymes

Coadministration of Iclusig with strong CYP3A inducers was not evaluated *in vitro* or in a clinical trial; however, a reduction in ponatinib exposure is likely *[see Clinical Pharmacology (12.3)]*. Coadministration of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's Wort) with Iclusig should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Monitor patients for signs of reduced efficacy.

7.3 Drugs That Elevate Gastric pH

Coadministration of Iclusig with drugs that elevate the gastric pH was not evaluated in a clinical trial. Based on the chemical properties of ponatinib, elevated gastric pH may reduce bioavailability and exposure *[see Clinical Pharmacology (12.3)]*. Coadministration of Iclusig with drugs that elevate the gastric pH (e.g., proton pump inhibitors, H2 blockers, or antacids) should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Monitor patients for signs of reduced efficacy.

7.4 Drugs That Are Substrates of the P-gp or ABCG2 Transporter Systems

In vitro studies demonstrate that Iclusig inhibits the P-gp and ABCG2 [also known as BCRP] transporter systems. The effect of coadministration of Iclusig with sensitive substrates of the P-gp (e.g., aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, tolvaptan, topotecan) and ABCG2 [also known as BCRP] (e.g., methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan) transporter systems on exposure of these substrates has not been evaluated in clinical studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

Based on its mechanism of action and findings in animals, Iclusig can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies with Iclusig in pregnant women. Advise women to avoid becoming pregnant while taking Iclusig. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal Data

Ponatinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 0.3, 1, and 3 mg/kg/day during organogenesis. At the maternally toxic dose of 3 mg/kg/day (equivalent to the AUC in patients receiving the recommended dose of 45 mg/day), ponatinib caused embryo-fetal toxicity as shown by increased resorptions, reduced body weight, external alterations, multiple soft tissue and skeletal alterations, and reduced ossification. Embryo-fetal toxicities also were observed at 1 mg/kg/day (approximately 24% the AUC in patients receiving the recommended dose) and involved multiple fetal soft tissue and skeletal alterations, including reduced ossification.

8.3 Nursing Mothers

It is unknown whether ponatinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ponatinib, a decision should be made whether to discontinue nursing or to discontinue Iclusig, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Iclusig in patients less than 18 years of age have not been established.

8.5 Geriatric Use

One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (38%) as compared with patients < 65 years of age (64%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a higher major hematologic response rate (47%) as compared with patients < 65 years of age (40%). Forty-six percent of patients ≥ 65 years had vascular occlusion events. Patients of age ≥ 65 years are more likely to experience adverse reactions including vascular occlusion decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Iclusig has not been studied in patients with hepatic impairment.

As hepatic elimination is a major route of excretion for Iclusig, hepatic impairment may result in increased ponatinib exposure. Avoid Iclusig in patients with moderate to severe (Child-Pugh B or C) hepatic impairment unless the benefit outweighs the possible risk of ponatinib overexposure *[see Clinical Pharmacology (12.3)]*. Patients with moderate to severe hepatic impairment may be at increased risk for adverse reactions *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Iclusig has not been studied in patients with renal impairment. Although renal excretion is not a major route of ponatinib elimination, the potential for moderate or severe renal impairment to affect hepatic elimination has not been determined *[see Clinical Pharmacology (12.3)]*.

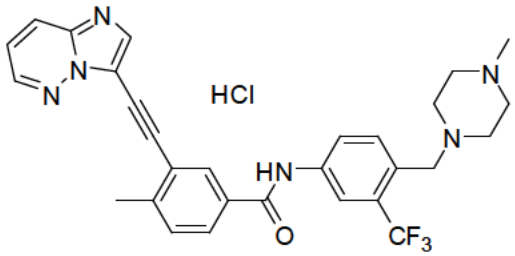
10 OVERDOSAGE

Overdoses with Iclusig were reported in clinical trials. One patient was accidentally administered the entire contents of a bottle of study medication via nasogastric tube. The investigator estimated that the patient received 540 mg of Iclusig. Two hours after the overdose, the patient had an uncorrected QT interval of 520 ms. Subsequent ECGs showed normal sinus rhythm with uncorrected QT intervals of 480 and 400 ms. The patient died 9 days after the overdose from pneumonia and sepsis. Another patient accidentally self-administered 165 mg on cycle 1 day 2. The patient experienced fatigue and non-cardiac chest pain on day 3. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and a moderate pericardial effusion.

In the event of an overdose of Iclusig, stop Iclusig, observe the patient and provide appropriate supportive treatment.

11 DESCRIPTION

Iclusig (ponatinib) is a kinase inhibitor. The chemical name for ponatinib hydrochloride is 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride. The molecular formula is $C_{29}H_{28}ClF_3N_6O$ which corresponds to a formula weight of 569.02 g/mol. Its structure is shown below:



Ponatinib HCl is an off-white to yellow powder with pKa of 2.77 and 7.8. The solubility of ponatinib in pH 1.7, 2.7, and 7.5 buffers is 7790 mcg/ml, 3.44 mcg/ml, and 0.16 mcg/ml, respectively, indicating a decrease in solubility with increasing pH. Iclusig tablets are available as white, round, film-coated tablets for oral administration. Each tablet contains ponatinib hydrochloride equivalent to 15 or 45 mg ponatinib with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide, magnesium stearate and a tablet coating. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ponatinib is a kinase inhibitor. Ponatinib inhibited the *in vitro* tyrosine kinase activity of ABL and T315I mutant ABL with IC_{50} concentrations of 0.4 and 2.0 nM, respectively. Ponatinib inhibited the *in vitro* activity of additional kinases with IC_{50} concentrations between 0.1 and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Ponatinib inhibited the *in vitro* viability of cells expressing native or mutant BCR-ABL, including T315I. In mice, treatment with ponatinib reduced the size of tumors expressing native or T315I mutant BCR-ABL when compared to controls.

12.2 Pharmacodynamics

In a cell-based assay, ponatinib concentrations of 20 nM (10.65 ng/mL) were sufficient to suppress most BCR-ABL mutant clones. However, ponatinib concentrations of 40 nM (21.3 ng/mL) were required to suppress T315I mutants. The median and range of steady-state C_{max} and trough (C_{min}) concentrations of ponatinib following 29 days of once-daily dosing of 15 mg, 30 mg and 45 mg are listed in Table 9.

Table 9: Median, Maximum, and Minimum Ponatinib Exposure at Steady-State by Dose Group: PK Evaluable Population

Dose	Median C_{max} (Range) (nM)	Median C_{min} (Range) (nM)
15 mg QD (n = 8)	49 (23 – 105)	28 (11 – 68)
30 mg QD (n = 9)	125 (67 – 178)	54 (41 – 89)
45 mg QD (n = 21)	161 (64 – 336)	67 (22 – 137)

Concentrations of ponatinib shown in cell-based assays to suppress unmutated BCR-ABL and most mutant BCR-ABL clones may be achieved at once daily dosing of 15 mg or 30 mg.

The dose intensity-safety relationship indicated that there are significant increases in grade ≥ 3 adverse events (hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) over the dose range of 15 to 45 mg once-daily.

12.3 Pharmacokinetics

The geometric mean (CV%) C_{max} and $AUC_{(0-\tau)}$ of Iclusig 45 mg daily at presumed steady state in patients with advanced hematologic malignancies were 73 ng/mL (74%) and 1253 ng•hr/mL (73%), respectively. Ponatinib administered as an investigational capsule formulation to patients with cancer exhibited approximately dose proportional increases in both C_{max} and AUC over the dose range of 15 to 60 mg. A dose intensity safety analysis showed a significant increase in grade 3 or higher adverse reactions (i.e., thrombocytopenia, neutropenia, rash, ALT elevation, AST elevation, pancreatitis, and lipase elevation) with an increase in dose intensity.

Absorption

The absolute bioavailability of ponatinib is unknown. Peak concentrations of ponatinib are observed within 6 hours after Iclusig oral administration. Following ingestion of either a high-fat or low-fat meal by 22 healthy volunteers, plasma ponatinib exposures (AUC and C_{max}) were not different when compared to fasting conditions. The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility *[see Description (11)]*. Drugs that elevate the gastric pH may reduce ponatinib bioavailability *[see Drug Interactions (7.3)]*.

Distribution

Ponatinib is greater than 99% bound to plasma proteins *in vitro*. The geometric mean (CV%) apparent steady state volume of distribution is 1223 liters (102%) following oral administration of Iclusig 45 mg once daily for 28 days in patients with cancer. Ponatinib is a weak substrate for both P-gp and ABCG2 [also known as BCRP] *in vitro*. Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT1) *in vitro*.

Metabolism

At least 64% of a ponatinib dose undergoes phase I and phase II metabolism. CYP3A4 and to a lesser extent CYP2C8, CYP2D6 and CYP3A5 are involved in the phase I metabolism of ponatinib *in vitro.* Ponatinib is also metabolized by esterases and/or amidases.

Elimination

The geometric mean (range) terminal elimination half-life of ponatinib was approximately 24 (12 to 66) hours following Iclusig 45 mg oral administration once daily for 28 days in patients with cancer. Exposure increased by approximately 90% (median) [range: 20% to 440%] between the first dose and presumed steady state. Ponatinib is mainly eliminated via feces. Following a single oral dose of [^{14}C]-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine.

Drug Interactions

Coadministration of Ponatinib and CYP3A Inhibitors

Coadministration of a single 15 mg oral dose of ponatinib in the presence of ketoconazole (400 mg daily), a strong CYP3A inhibitor, to 22 healthy volunteers, increased the $AUC_{0-\infty}$ and C_{max} of ponatinib by 78% and 47%, respectively, when compared to administration of ponatinib alone *[see Drug Interactions (7.1)]*.

Coadministration of Ponatinib and CYP3A Inducers

Since the human oxidative metabolism of ponatinib via the cytochrome P450 system primarily involves CYP3 isozymes, a reduction in ponatinib exposure is likely and was observed in simulations using a mechanistic model *[see Drug Interactions (7.2)]*.

Coadministration With Other CYP Substrates

In vitro studies indicate that ponatinib does not inhibit the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, or CYP2D6 and does not induce the metabolism of substrates for CYP1A2, CYP2B6, or CYP3A.

Coadministration With Substrates of Transporters

In vitro, ponatinib is an inhibitor of P-gp and ABCG2 [also known as BCRP], and BSEP *[see Drug Interactions (7.4)]*.

In vitro, ponatinib did not inhibit the human organic anion transporting polypeptides OATP1B1 or OATP1B3, or the organic cation transporters OCT1, OCT2, OAT1, and OAT3.

Pharmacokinetics in Specific Populations

Hepatic Impairment

Iclusig has not been studied in patients with hepatic impairment. As hepatic elimination is a major route of excretion for ponatinib, hepatic impairment may result in increased plasma ponatinib concentrations *[see Use in Specific Populations (8.6)]*.

Renal Impairment

Iclusig has not been studied in patients with renal impairment. Although renal excretion is not a major route of ponatinib elimination, the potential for moderate or severe renal impairment to affect hepatic elimination has not been determined *[see Use in Specific Populations (8.7)]*.

12.6 QT/QTc Prolongation

A QT assessment was performed in 39 patients with cancer who received 30 mg, 45 mg, or 60 mg Iclusig once daily. No large changes in the mean QTc interval (i.e., > 20 ms) from baseline were detected in the study. However, a small increase in the mean QTc interval (i.e., < 10 ms) cannot be excluded because of study design limitations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ponatinib.

Ponatinib was not mutagenic in a bacterial mutagenesis (Ames) assay, was not clastogenic in a chromosome aberration assay in human lymphocytes, nor was it clastogenic in an *in vivo* mouse micronucleus assay at oral doses up to 2000 mg/kg.

Ponatinib may impair male and female fertility. Fertility studies using ponatinib were not conducted. However, ponatinib effects on male and female reproductive organs observed during general toxicology studies included degeneration of epithelium of the testes in rats and monkeys and follicular atresia in the monkey ovary with associated endometrial atrophy. Effects seen in rats were at exposures approximating the AUC in patients receiving the recommended dose of 45 mg/day and in monkeys were approximately 4 times the AUC in patients.

14 CLINICAL STUDIES

The safety and efficacy of Iclusig in patients with CML and Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy were evaluated in a single-arm, open-label, international, multicenter trial. Efficacy results described below should be interpreted within the context of updated safety information *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precaution (5.1, 5.2)]*

All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; or blast phase CML /Philadelphia-positive acute lymphoblastic leukemia [BP-CML]/Ph+ ALL), resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation.

Resistance in CP-CML while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML, and by 1 month in BP-CML and Ph+ ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy.

Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with AP-CML, BP-CML, or Ph+ ALL.

The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary efficacy endpoint in AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL).

The trial enrolled 449 patients, of which 444 were eligible for efficacy analysis: 267 patients with CP-CML (R/I Cohort: n=203, T315I: n=64), 83 patients with AP-CML, 62 patients with BP-CML, and 32 patients with Ph+ ALL. Five patients were not eligible for efficacy analysis due to lack of confirmation of T315I mutation status, and these patients had not received prior dasatinib or nilotinib.

At the time of analysis, the median follow-up was 10 months (minimum of 6 months of follow-up for all ongoing patients). Baseline demographic characteristics are described in Table 10.

Table 10: Demographic and Disease Characteristics

Patient Characteristics at Entry	**Efficacy Population N=444**
Age	
Median, years (range)	59 (18 to 94)
Gender, n (%)	
Male	236 (53%)
Race, n (%)	
Asian	57 (13%)
Black or African American	25 (6%)
White	349 (79%)
Other	13 (3%)
ECOG Performance Status, n (%)	
ECOG=0 or 1	409 (92%)
Disease History	
Median time from diagnosis to first dose, years (range)	6.1 (0.3 to 28.5)
Resistant to Prior TKI Therapy, n (%)	374 (88%)
Presence of one or more BCR-ABL kinase domain mutations*	244 (55%)
Prior TKI therapy– number of prior approved TKIs, n (%)	
1	29 (7%)
2	166 (37%)
≥3	249 (56%)

*Of the patients with one or more BCR-ABL kinase domain mutations detected at entry, 37 unique mutations were detected.

At the time of analysis, the median duration of Iclusig treatment was 281 days in patients with CP-CML, 286 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ ALL. Efficacy results are summarized in Table 11, and Table 12.

Table 11: Efficacy of Iclusig in Patients With Resistant or Intolerant Chronic Phase CML

	Overall (N=267)	**Cohort**	
		R/I Cohort (N=203)	**T315I Cohort (N=64)**
Cytogenetic Response			
Major[a] (MCyR) % (95% CI)	 54% (48,60)	 49% (42,56)	 70% (58,81)
Complete (CCyR) % (95% CI)	 44% (38,50)	 37% (31,44)	 66% (53,77)

[a] Primary endpoint for CP-CML Cohorts was MCyR, which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

In patients with CP-CML patients who achieved MCyR, the median time to MCyR was 84 days (range: 49 to 334 days). At the time of analysis, the median durations of MCyR had not yet been reached.

Table 12: Efficacy of Iclusig in Patients With Resistant or Intolerant Advanced Disease (includes R/I and T315I cohorts)

	AP-CML Overall (N=83)	**BP-CML Overall (N=62)**	**Ph+ ALL Overall (N=32)**
Hematologic Response			
Major[a] (MaHR) % (95% CI)	 52% (41,63)	 31% (20,44)	 41% (24,59)
Complete[b] (CHR) % (95% CI)	 47% (33,55)	 21% (12,33)	 34% (19,53)

[a] Primary endpoint for patients with AP-CML, BP-CML, and Ph+ ALL was MaHR, which combines complete hematologic responses and no evidence of leukemia.

[b] CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).

The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 21 days (range: 12 to 176 days), 29 days (range 12 to 113 days), and 20 days (range: 11 to 168 days), respectively. The median duration of MaHR for patients with AP-CML, BP-CML, and Ph+ ALL was 9.5 months (range: 1.1 to 17.7 months), 4.7 months (range: 1.8 to 14.1+ months), and 3.2 months (range: 1.8 to 8.8+ months), respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

Iclusig tablets are available in the following configurations:

Strength	NDC Number	Description	Presentation
15 mg	76189-535-60	round, white, film-coated tablets with debossed “A5” on one side and plain on the other side	60 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner
	76189-535-80		180 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner
45 mg	76189-534-30	round, white, film-coated tablets with debossed “AP4” on one side and plain on the other side	30 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner
	76189-534-90		90 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner

Iclusig tablets should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. Keep away from children.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

Advise patients of the following and provide a copy of the Medication Guide:

Vascular Occlusions

Inform patients that serious arterial thromboses (including arterial stenosis sometimes requiring revascularization) and venous thromboembolism events have occurred. Advise patients to immediately contact their health care provider with any symptoms suggestive of a blood clot such as chest pain, shortness of breath, weakness on one side of the body, speech problems, leg pain, or leg swelling *[see Warnings and Precautions (5.1)]*.

Heart Failure and Cardiac Arrhythmias

Inform patients of the possibility of heart failure, and abnormally slow or fast heart rates. Advise patients to contact their health care provider if they experience symptoms such as shortness of breath, chest pain, palpitations, dizziness, or fainting *[see Warnings and Precautions (5.2, 5.10)]*.

Hepatotoxicity

Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately contact their health care provider if signs of liver failure occur, including yellowing of the eyes or skin, “tea”-colored urine, or drowsiness *[see Warnings and Precautions (5.3)]*.

Hypertension

Inform patients of the possibility of new or worsening of existing hypertension. Advise patients to contact their health care provider for elevated blood pressure or if symptoms of hypertension occur including headache, dizziness, chest pain, or shortness of breath *[see Warnings and Precautions (5.4)]*.

Pancreatitis

Inform patients of the possibility of developing pancreatitis that may be accompanied by nausea, vomiting, abdominal pain, or abdominal discomfort, and to promptly report these symptoms *[see Warnings and Precautions (5.5)]*.

Neuropathy

Inform patients of the possibility of developing peripheral or cranial neuropathy while being treated with Iclusig. Advise patients to report symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness *[see Warnings and Precautions (5.6)]*.

Ocular Toxicity

Inform patients of the possibility of ocular toxicity while being treated with Iclusig. Advise patients to report symptoms of ocular toxicity, such as blurred vision, dry eye, or eye pain *[see Warnings and Precautions (5.7)]*.

Hemorrhage

Inform patients of the possibility of serious bleeding and to immediately contact their health care provider with any signs or symptoms suggestive of hemorrhage such as unusual bleeding or easy bruising *[see Warnings and Precautions (5.8)]*.

Fluid Retention

Inform patients of the possibility of developing fluid retention and to contact their health care provider for symptoms such as leg swelling, abdominal swelling, weight gain, or shortness of breath *[see Warnings and Precautions (5.9)]*.

Myelosuppression

Inform patients of the possibility of developing low blood cell counts; inform patients to report immediately should fever develop, particularly in association with any suggestion of infection *[see Warnings and Precautions (5.11)]*.

Compromised Wound Healing and Gastrointestinal Perforation

Advise patients to inform their health care provider if they plan to undergo a surgical procedure or had recent surgery *[see Warnings and Precautions (5.13)]*.

Inform patients that cases of gastrointestinal perforation have been reported *[see Warnings and Precautions (5.13)]*.

Embryo-Fetal Toxicity

Inform patients that Iclusig can cause fetal harm when administered to a pregnant woman. Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.1)]*.

Instructions for Taking Iclusig

Advise patients to take Iclusig exactly as prescribed and not to change their dose or to stop taking Iclusig unless they are told to do so by their health care provider. Iclusig may be taken with or without food. Iclusig tablets should be swallowed whole. Patients should not crush or dissolve the tablets.

Patients should not take two doses at the same time to make up for a missed dose.

Lactose

Inform patients that Iclusig contains 121 mg of lactose monohydrate in a 45 mg daily dose.

Manufactured for:

ARIAD Pharmaceuticals, Inc.

26 Landsdowne Street

Cambridge, MA 02139-4234

MEDICATION GUIDE

Iclusig® (eye-CLUE-sig)

(ponatinib)

Tablets

What is the most important information I should know about Iclusig?

Iclusig can cause serious side effects, including:

Blood clots or blockage in your blood vessels (arteries and veins). Blood clots or blockage in your blood vessels may lead to heart attack, stroke, or death. A blood clot or blockage in your blood vessels can prevent proper blood flow to your heart, brain, bowels (intestines), legs, eyes, and other parts of your body. You may need emergency surgery or treatment in a hospital. Get medical help right away if you get any of the following symptoms:

- chest pain or pressure
- pain in your arms, legs, back, neck or jaw
- shortness of breath
- numbness or weakness on one side of your body
- trouble talking
- headache
- dizziness
- severe stomach area pain
- decreased vision or loss of vision

Blood clots or blockage in your blood vessels can happen in people with or without risk factors for heart and blood vessel disease, including people 50 years of age or younger. Talk to your healthcare provider if this is a concern for you.

Heart problems. Iclusig can cause heart problems, including heart failure which can be serious and may lead to death. Heart failure means your heart does not pump blood well enough. Iclusig can also cause irregular slow or fast heartbeats and heart attack. Your healthcare provider will check your heart function before and during your treatment with Iclusig. Get medical help right away if you get any of the following symptoms: shortness of breath, chest pain, fast or irregular heartbeats, dizziness, or feel faint.

Liver problems. Iclusig can cause liver problems, including liver failure, which can be severe and may lead to death. Your healthcare provider will do blood tests before and during your treatment with Iclusig to check for liver problems. Get medical help right away if you get any of these symptoms of liver problems during treatment:

- yellowing of your skin or the white part of your eyes (jaundice)
- dark “tea-colored” urine
- sleepiness

See **“What are the possible side effects of Iclusig?”** for information about side effects.

What is Iclusig?

Iclusig is a prescription medicine used to treat adults who have:

- a specific type of abnormal gene (T315I-positive) chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML), or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
- chronic phase, accelerated phase, or blast phase CML or Ph+ ALL who cannot receive any other tyrosine kinase inhibitor (TKI) medicines

It is not known if Iclusig is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before taking Iclusig?

Before you take Iclusig, tell your healthcare provider if you:

- have a history of blood clots in your blood vessels (arteries or veins)
- have heart problems, including heart failure, irregular heartbeats, and QT prolongation
- have diabetes
- have a history of high cholesterol
- have liver problems
- have had inflammation of your pancreas (pancreatitis)
- have high blood pressure
- have bleeding problems
- plan to have any surgical procedures
- are lactose (milk sugar) intolerant. Iclusig tablets contain lactose.
- drink grapefruit juice
- have any other medical conditions
- are pregnant or plan to become pregnant. Iclusig can harm your unborn baby. You should not become pregnant while taking Iclusig. Tell your healthcare provider right away if you become pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Iclusig passes into your breast milk. You and your healthcare provider should decide if you will take Iclusig or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription medicines and over-the-counter medicines, vitamins, and herbal supplements. Iclusig and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Iclusig?

- Take Iclusig exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose of Iclusig or tell you to stop taking Iclusig.
- Do not change your dose or stop taking Iclusig without talking to your healthcare provider.
- Swallow Iclusig tablets whole. Do not crush or dissolve Iclusig tablets.
- You may take Iclusig with or without food.
- If you miss a dose of Iclusig, take your next dose at your regular time. Do not take 2 doses at the same time to make up for a missed dose.
- If you take too much Iclusig, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of Iclusig?

Iclusig may cause serious side effects, including:

- See **"What is the most important information I should know about Iclusig?"**
- **High blood pressure**. Your blood pressure should be checked regularly and any high blood pressure should be treated while you are taking Iclusig. Tell your healthcare provider if you get headaches, dizziness, chest pain or shortness of breath.
- **Inflammation of the pancreas (pancreatitis).** Symptoms include sudden stomach-area pain, nausea, and vomiting. Your healthcare provider should do blood tests to check for pancreatitis during treatment with Iclusig.
- **Neuropathy.** Iclusig may cause damage to the nerves in your arms, brain, hands, legs, or feet (Neuropathy). Tell your healthcare provider if you get any of these symptoms during treatment with Iclusig:
    - muscle weakness, tingling, burning, pain, and loss of feeling in your hands and feet
    - double vision and other problems with eye sight, trouble moving the eye, drooping of part of the face, sagging or drooping eyelids
- **Effects on the eye.** Serious eye problems that can lead to blindness or blurred vision may happen with Iclusig. Tell your healthcare provider if you get any of the following symptoms: perceived flashes of light, light sensitivity, floaters, dry or itchy eyes, and eye pain. Your healthcare provider will monitor your vision before and during your treatment with Iclusig.
- **Severe bleeding.** Iclusig can cause bleeding which can be serious and may lead to death. Tell your healthcare provider if you get any signs of bleeding while taking Iclusig including:
    - vomiting blood or if your vomit looks like coffee-grounds

- pink or brown urine
- red or black (looks like tar) stools
- coughing up blood or blood clots
- unusual bleeding or bruising of your skin
- menstrual bleeding that is heavier than normal
- unusual vaginal bleeding
- nose bleeds that happen often
- drowsiness or difficulty being awakened
- confusion
- headache
- change in speech

- **Fluid retention.** Your body may hold too much fluid (fluid retention). Tell your healthcare provider right away if you get any of these symptoms during treatment with Iclusig:
  - swelling of your hands, ankles, feet, face, or all over your body
  - weight gain
  - shortness of breath and cough
- **Low blood cell counts.** Iclusig may cause low blood cell counts. Your healthcare provider will check your blood counts regularly during treatment with Iclusig. Tell your healthcare provider right away if you have a fever or any signs of an infection while taking Iclusig.
- **Tumor Lysis Syndrome (TLS). TLS** is caused by a fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - an abnormal heartbeat

  Your healthcare provider may do blood tests to check for TLS.
- **Possible wound healing problems.** If you need to have a surgical procedure, tell your healthcare provider that you are taking Iclusig. You should stop taking Iclusig at least 1 week before any planned surgery.
- **A tear in your stomach or intestinal wall (perforation).** Tell your healthcare provider right away if you get:
  - severe pain in your stomach-area (abdomen)
  - swelling of the abdomen
  - high fever

The most common side effects of Iclusig include:

- skin rash
- stomach-area (abdomen) pain
- tiredness
- headache
- dry skin
- constipation
- fever
- joint pain
- nausea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of Iclusig. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Iclusig?

Store Iclusig at room temperature between 68°F to 77°F (20°C to 25°C).

Keep Iclusig and all medicines out of the reach of children.

General information about Iclusig

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Iclusig for a condition for which it was not prescribed. Do not give Iclusig to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about Iclusig that is written for health professionals.

For more information, go to www.iclusig.com or call 1-855-552-7423.

What are the ingredients in Iclusig?

Active ingredient: ponatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide and magnesium stearate. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
ARIAD Pharmaceuticals, Inc.
26 Landsdowne Street
Cambridge, MA 02139-4234

Revised: December 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

REMS

REMS Document
Initial Approval 12/2013

NDA 203469

Iclusig® (ponatinib) tablets
Drug Class: Tyrosine Kinase Inhibitor

ARIAD Pharmaceuticals, Inc.
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Risk Evaluation and Mitigation Strategy (REMS)

I. GOALS

The goals of the Iclusig REMS are to:

- Inform prescribers of the indications for Iclusig which are limited to:
  - Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
  - Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
- Inform prescribers of the serious risk of vascular occlusion and thromboembolism associated with Iclusig treatment.

II. REMS ELEMENTS

A. Communication Plan

ARIAD will implement the following communication plan for Healthcare Providers who are likely to prescribe Iclusig. This communication plan will consist of the following:

1. REMS Letter - *REMS Letter to Healthcare Providers* will be sent within 21 days after the REMS approval date, and will be distributed electronically or by mail to hematologists and oncologists and to other Healthcare Providers known or likely to be Iclusig prescribers. If a targeted Healthcare Provider's email address is not available, or if an email is undeliverable, the provider will receive the letter through the mail. The *REMS Letter to Healthcare Providers* will inform Healthcare Providers of the approved indications for Iclusig and the serious risk of vascular occlusion and thromboembolism associated with Iclusig. The letter will be accompanied by the

Prescribing Information (PI) and the *Iclusig REMS Fact Sheet*. The letter will be available from the *Iclusig REMS Website* (www.IclusigREMS.com) at the time of distribution and will remain on the website for the duration of the REMS.

2. REMS Letter for Professional Societies - A *REMS Letter for Professional Societies* will be distributed within 21 days after the REMS approval date. The letter will be distributed electronically or by mail. The *REMS Letter for Professional Societies* will inform the leadership of the professional societies described below of the approved indications for Iclusig and of the serious risk of vascular occlusion and thromboembolism associated with Iclusig. The leadership of the professional societies will be asked to distribute this information to their memberships.

The *REMS Letters for Professional Societies* will be distributed to the following organizations:

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- Oncology Nursing Society (ONS)
- National Comprehensive Cancer Network (NCCN)
- Hematology Oncology Pharmacy Association (HOPA)
- American Pharmacists Association (APhA)
- American Society of Health-System Pharmacists (ASHP)

The letter will be sent to MedWatch at the same time it is sent to the Professional Societies.

3. REMS Fact Sheet - An *Iclusig REMS Fact Sheet* will be available for Healthcare Providers. The *Iclusig REMS Fact Sheet* will be included in the mailings of the *REMS Letter to Healthcare Providers* and the *REMS Letter for Professional Societies* and will be available on the Iclusig REMS website (www.IclusigREMS.com). Hard copies of the *Iclusig REMS Fact Sheet* will also be distributed by ARIAD's sales representatives and medical field-based personnel to Healthcare Providers during follow-up details/visits with Healthcare Providers for the first 12 months after the approval of the Iclusig REMS.

4. Journal Information Piece - ARIAD will publish in the following professional journals an information piece that includes the approved indications for Iclusig and the serious risk of vascular occlusion and thromboembolism associated with Iclusig:

- Journal of Clinical Oncology
- Blood
- New England Journal of Medicine
- Hematology Oncology
- US Oncology & Hematology

The information piece will be published quarterly in each publication for one year following the REMS approval.

5. Scientific Meetings - The *Iclusig REMS Fact Sheet* and the Prescribing Information, will be prominently displayed at scientific meetings where ARIAD has a presence (e.g., booth) for one year following the REMS approval.

6. Iclusig REMS Website - The *Iclusig REMS Website* will be available within 15 days after the REMS approval date. The website (www.IclusigREMS.com) will contain information on the Iclusig REMS and will provide access to all the REMS materials, and the US Prescribing Information. The website will be available for the duration of the REMS.

The following are part of the REMS and are appended.

- The *REMS Letter to Healthcare Providers*(print and email version)
- The *REMS Letter for Professional Societies* (print and email version)
- The *REMS Fact Sheet*
- The Journal Information Piece
- The *Iclusig REMS Website* (Landing Page)

B. Timetable for Submission of Assessments

ARIAD will submit REMS assessments to FDA 1 year, 3 years and 7 years from the date of initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. ARIAD will submit each assessment so that it will be received by the FDA on or before the due date.

ICLUSIG®
(ponatinib) tablets

Iclusig® REMS

FDA REQUIRED REMS SAFETY INFORMATION

Iclusig® (ponatinib)
- **Revised indications**
- **New safety information about risk of vascular occlusion**
- **New dosing considerations**

<Date>

IMPORTANT SAFETY UPDATE

Dear Healthcare Provider:

The FDA has required this update as part of the Iclusig REMS (**R**isk **E**valuation and **M**itigation **S**trategy) to inform Healthcare Providers about the following **labeling updates** and **serious risks of Iclusig**:

- **Revised indications have been limited to:**
  - Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
  - Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated

- **New safety information about risk of vascular occlusion in Boxed Warning**
  - Arterial and venous thrombosis and occlusions have occurred in at least **27%** of Iclusig clinical trial patients

- **New dosing considerations**
  - **Optimal dosing has not been identified**. In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy

Please see the nonpromotional fact sheet, reviewed by the FDA, with more detailed safety information, enclosed.

This letter does not contain the complete safety profile for Iclusig. Please review the Prescribing Information, including Boxed Warning, and Medication Guide, enclosed.

ICLUSIG®
(ponatinib) tablets

Iclusig® REMS

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with Iclusig to the FDA or to ARIAD at 1-855-552-7423 or send the information to ARIAD at medinfo@ariad.com.

Sincerely,

Frank G. Haluska, MD, PhD
Chief Medical Officer
Senior Vice President, Clinical Research and Development
ARIAD Pharmaceuticals, Inc.

ARIAD

ICLUSIG®
(ponatinib) tablets

Iclusig® REMS

FDA REQUIRED REMS SAFETY INFORMATION

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Please see the nonpromotional fact sheet, reviewed by the FDA, with more detailed safety information: Iclusig REMS Fact Sheet
You may also visit www.iclusigREMS.com for more information.

This letter does not contain the complete safety profile for Iclusig. To review the Prescribing Information, including complete Boxed Warning and Medication Guide, see links below:
Prescribing Information Medication Guide

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Iclusig® REMS

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ARIAD

ICLUSIG®
(ponatinib) tablets

Iclusig® REMS

FDA REQUIRED REMS SAFETY INFORMATION

Iclusig® (ponatinib)
- **Revised indications**
- **New safety information about risk of vascular occlusion**
- **New dosing considerations**

<Date>

<Name, MD>
<Address>
<City, State, Zip>

<Dear Dr. NAME:>

IMPORTANT SAFETY UPDATE

The FDA has required ARIAD Pharmaceuticals, Inc., to distribute this update to the [Professional Organization] as part of their Iclusig REMS (Risk Evaluation and Mitigation Strategy) program. We request that you inform your members about the following **labeling updates** and **serious risks of Iclusig:**

- **Revised indications have been limited to:**
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Iclusig® REMS

A nonpromotional fact sheet, reviewed by the FDA, with more detailed safety information is enclosed, and also available at: www.iclusigREMS.com/factsheet.pdf

This letter does not contain the complete safety profile for Iclusig® (ponatinib). Please visit www.iclusigREMS.com for more information.

Sincerely,

Frank G. Haluska, MD, PhD
Chief Medical Officer
Senior Vice President, Clinical Research and Development
ARIAD Pharmaceuticals, Inc.

ARIAD

ICLUSIG®
(ponatinib) tablets

Iclusig® REMS

FDA REQUIRED REMS SAFETY INFORMATION

Iclusig® (ponatinib)
- **Revised indications**
- **New safety information about risk of vascular occlusion**
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<Date>

<Name, MD>
<Address>
<City, State, Zip>

<Dear Dr. NAME:>

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Iclusig® REMS

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www.iclusigREMS.com

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Sincerely,

Frank G. Haluska, MD, PhD
Chief Medical Officer
Senior Vice President, Clinical Research and Development
ARIAD Pharmaceuticals, Inc.

ARIAD

ICLUSIG®
(ponatinib) tablets

New Labeling and Safety Information for Iclusig® (ponatinib)

Iclusig® (ponatinib)
- **Revised indications**
- **New safety information about risk of vascular occlusion**
- **New dosing considerations**

REVISED INDICATIONS

The indications have been limited to:
- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated

UPDATED SERIOUS RISK OF VASCULAR OCCLUSION IN BOXED WARNING

Arterial and venous thrombosis and occlusions have occurred in at least **27%** of all Iclusig clinical trial patients, including:
- Fatal myocardial infarction
- Stroke
- Stenosis of large arterial vessels of the brain
- Severe peripheral vascular disease, and
- Need for urgent revascularization procedures

Iclusig can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion (see Table 1).

Table 1: Vascular Occlusion Incidence in Iclusig-Treated Patients in Phase 2 Trial According to Risk Categories

	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia	No history of ischemia, hypertension, diabetes, or hyperlipidemia
Age: 49 or younger	18% (6/33)	12% (13/112)
Age: 50 to 74 years	33% (50/152)	18% (20/114)
Age: 75 and older	56% (14/25)	46% (6/13)
All age groups	33% (70/210)	16% (39/239)
Total	24% (109/449)	

ICLUSIG®
(ponatinib) tablets

DOSING CONSIDERATIONS

Optimal dosing has not been identified.

In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.

Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for chronic phase CML (CP-CML) and accelerated phase CML (AP-CML) patients who have achieved a major cytogenetic response.

Consider discontinuing Iclusig if response has not occurred by 3 months (90 days).

Do not restart Iclusig in patients with arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options.

OTHER SERIOUS RISKS INCLUDED IN THE BOXED WARNING

- **Heart failure**, including fatalities, occurred in 8% of Iclusig-treated patients.
  Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure

- **Hepatotoxicity**, liver failure and death have occurred in Iclusig-treated patients.
  Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected

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WHAT IS THE ICLUSIG REMS?

A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The purpose of the Iclusig REMS is to inform Healthcare Providers of new important safety information in the revised Iclusig label, including serious risks of Iclusig. This fact sheet is required by the FDA as part of the Iclusig REMS program.

Please visit www.iclusigREMS.com for further information.

This fact sheet does not contain the complete safety profile for Iclusig. Please see the Prescribing Information, including Boxed Warning and Medication Guide.

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with Iclusig to the FDA or to ARIAD at 1-855-552-7423 or send the information to ARIAD at medinfo@ariad.com.

ARIAD®

Reference ID: 3425782

ICLUSIG®
(ponatinib) tablets

New Labeling and Safety Information for Iclusig® (ponatinib)

REVISED INDICATIONS

The indications have been limited to:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other available tyrosine kinase inhibitor (TKI) is indicated

UPDATED SERIOUS RISK OF VASCULAR OCCLUSION IN BOXED WARNING

Arterial and venous thrombosis and occlusions have occurred in at least 27% of all Iclusig clinical trial patients, **including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures.**

Iclusig can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion (see Table 1).

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Total	24% (109/449)	

DOSING CONSIDERATIONS

Optimal dosing has not been identified.

In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.

Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for chronic phase CML (CP-CML) and accelerated phase CML (AP-CML) patients who have achieved a major cytogenetic response.

Consider discontinuing Iclusig if response has not occurred by 3 months (90 days).

Do not restart Iclusig in patients with arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options.

This journal piece is part of the FDA-required Iclusig REMS. Visit www.iclusigREMS.com for more information.

For complete safety information, see the Prescribing Information available at www.iclusigREMS.com.

Reference ID: 3425782

ICLUSIG® (ponatinib) tablets

IMPORTANT SAFETY INFORMATION | PRESCRIBING INFORMATION | MEDICATION GUIDE

Iclusig® (ponatinib) REMS

Iclusig REMS (Risk Evaluation and Mitigation Strategy)

A REMS is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product.

The purpose of the Iclusig REMS is to inform Healthcare Providers about the new safety information in the revised label including the serious risks of Iclusig. Safety updates include:

- Revised indications
- New safety information about serious risk of vascular occlusion
- New dosing considerations

Download and Print Resources

REMS Letter to Healthcare Providers
Download PDF
Iclusig® REMS Fact Sheet
Download PDF

REVISED INDICATIONS

The indications have been limited to:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
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Arterial and venous thrombosis and occlusions have occurred in at least **27%** of Iclusig clinical trial patients, including:

- Fatal myocardial infarction
- Severe peripheral vascular disease
- Stroke
- Need for urgent revascularization procedures
- Stenosis of the large arterial vessels of the brain

Iclusig can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events.

Table 1: Vascular Occlusion Incidence in Iclusig-Treated Patients in Phase 2 Trial According to Risk Categories

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Consider discontinuing Iclusig if response has not occurred by 3 months (90 days).

Do not restart Iclusig in patients with arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options.

WARNING: VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY

Vascular Occlusion:

- **Arterial and venous thrombosis and occlusions have occurred in at least 27% of Iclusig treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events.**
- **Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion. A benefit-risk consideration should guide a decision to restart Iclusig therapy.**

Heart Failure:

- **Heart failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure.**

Hepatotoxicity:

- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected.**

This site is intended for US Healthcare Professionals.

ARIAD®

Reference ID: 3425782

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
12/20/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

DIVISION DIRECTOR MEMO

Memorandum to File

Center for Drug Evaluation and Research
Food and Drug Administration

To: NDA 203469

From: Ann Farrell, M.D.
Director, Division of Hematology Products
Office of Hematology and Oncology Products

Date: December 19, 2013

Subject: Marketing Resumption for Iclusig (Ponatinib)

This memo supports the marketing resumption for Iclusig (Ponatinib).

Iclusig was initially granted accelerated approval on December 14, 2012 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. At the time of approval, the prescribing information included a Boxed Warning for arterial thrombosis and stated that cardiovascular, cerebrovascular, and other vascular thromboses, including fatal myocardial infarction and stroke have occurred in patients and that in clinical trials, serious arterial thrombosis occurred in 8% of patients treated with Iclusig. The labeling recommended the interruption and consideration of discontinuation of Iclusig in patients who develop arterial thrombotic events. The approval letter for Iclusig had several post-marketing requirements (PMRs) including one to provide longer term follow-up information.

Following approval, the product has been under routine post-marketing surveillance. Since then an increase in the frequency of vascular occlusive events including revascularizations has been noted prompting numerous correspondence and teleconferences between the Agency and Ariad Pharmaceuticals. On October 11, 2013, the Agency issued a Drug Safety Communication (DSC) informing the public of emerging information about the risk of vascular occlusive events.

Subsequently Ariad informed the Agency about the planned termination of their phase 3 trial (PMR 1984-8) due to higher than expected vascular occlusive adverse events. The purpose of this PMR was to provide a greater understanding of the longer term safety issues associated with Iclusig use. On October 30, 2013, the Agency asked Ariad to voluntarily suspend marketing and sales of the drug. The Agency decided that the suspension would facilitate Iclusig marketing resumption under different conditions of use and with more current

information regarding the risks and benefit in the labeling. Prior to the suspension the Agency and Ariad discussed a mechanism that would be in place to provide treatment to patients judged to be appropriate for therapy using an IND protocol. Ariad voluntarily suspended marketing on October 31, 2013. That same day, the Agency issued a second DSC to inform patients and healthcare providers that marketing and sales of the drug had been voluntarily suspended. The Agency determined that the requirements for new safety provisions under the Food and Drug Administration Amendments Act (FDAAA) was warranted and notified Ariad of the need for revised safety labeling, Risk Evaluation and Mitigation Strategies (REMS), and additional post-marketing requirements to further characterize safety and dosing. The Agency issued a letter to Ariad informing them of these requirements.

Since the voluntary suspension, divisions within the Agency and Ariad have worked to understand the data. Numerous Agency clinical, clinical pharmacology and statistical reviewers have spent significant effort reviewing and analyzing the available data. Our ability to fully understand the relationships of dosing, safety, exposure-response, and exposure-toxicity were limited by the small numbers of patients exposed to lower than the recommended doses. Retrospective data analyses are at best exploratory and we decided that these issues would best be addressed through prospective post-marketing requirements for additional study prospectively collecting response, adverse event, and pharmacokinetic data. Ariad has agreed to conduct additional post-marketing investigations.

For the past several weeks, the Agency and Ariad have worked to revise the labeling and Risk Evaluation and Mitigation Strategy. For revised labeling, the following sections of the Iclusig prescribing information were updated: the Boxed Warning, Indications and Usage, Dosage and Administration, and Warnings and Precautions. Due to data limitations, discussed above, the recommended starting dose will not be changed; however, there will be information on the percentage of patients who had to reduce their dose due to adverse events and a recommendation to consider a dose reduction. The REMs will include a multi-faceted communication of changes to the prescribing information and safety risks, using a combination of tools including a “Dear Healthcare Provider” letter, email, journal advertising, and REMS information webpage to inform prescribers of the revised indications for Iclusig and the serious risks of vascular occlusion and thromboembolism associated with treatment. Ariad has agreed to the Agency’s recommended six PMRs and recommendations for revised labeling which are included in the Agency’s December 2013 letter.

Ariad Pharmaceuticals will have a marketing resumption plan in place to allow a smooth transition particularly for those patients who were granted access to Iclusig under an eIND.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
12/19/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

MEDICAL REVIEW(S)

Clinical Memo- Increasing Vascular Occlusive Events with Iclusig (Ponatinib)

NDA	203469
Drug Name	Ponatinib (Iclusig)
Medical Officer	Nicole Verdun, MD
Medical Team Leader	R. Angelo De Claro, MD
Sponsor	ARIAD Pharmaceuticals, Inc.
Date	18 December 2013
Update	New Safety Concerns, Labeling Changes, Sponsor Interactions

Background

Iclusig (ponatinib) is a tyrosine kinase inhibitor *currently* indicated 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.

- Treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.

Ponatinib was given accelerated approval on December 14, 2012. When Iclusig® was approved, the prescribing information included a boxed warning for arterial thrombosis, noting "cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke have occurred in Iclusig-treated patients. In clinical trials, serious arterial thrombosis occurred in 8% of Iclusig-treated patients. Interrupt and consider discontinuation of Iclusig in patients who develop arterial thrombotic events."

Since the time of approval, Ariad Pharmaceuticals, Inc. has submitted serious adverse event (SAE) reports of vascular occlusive events, including fatal events. This prompted an updated review of the vascular occlusive event rate in patients treated with ponatinib. Additionally, the Sponsor has submitted SAE reports of neurotoxicity, prompting a review of the incidence of neurologic events. A new safety signal of ocular toxicity was also reported in SAEs, which is not currently included in the prescribing information.

Safety Update

Since Iclusig's approval, postmarketing adverse event reports and follow-up data from clinical trials have indicated an increasing frequency of vascular occlusive events, with involvement of additional vascular beds. Based on the increasing pattern and frequency of vascular occlusion events, DHP requested information and analyses by the Sponsor, including full datasets for FDA analysis. In addition, FDA held multiple meetings with Ariad to discuss the safety findings. FDA recommended that Ariad review all cases of vascular occlusive events that occurred in

patients treated with Iclusig and provide clarity with regards to the frequency and characterization of these events.

FDA conducted an independent analysis of the updated safety information. DHP's review identified substantial cumulative differences in safety outcomes since the time of approval. From that analysis, FDA noted differences with the Sponsor's approach to describing the frequency and severity of the vascular occlusion events. Some of the serious events including stroke were characterized as grade 1 (mild). A review of the non-serious events revealed concerning events such as myocardial infarction, extremity necrosis, and pulmonary embolism. In addition, FDA noted limitations on the use of investigator's attribution of "drug-relatedness", in a setting wherein there was no control arm or masking/blinding of the treatment assignments. Hence, FDA considered all vascular occlusion events in reporting the event rates.

The analyses showed serious adverse reactions have increased in frequency since the time of approval. Specifically, the analyses indicate that vascular occlusions have occurred in at least 27% of Iclusig treated patients in clinical trials (Phase 1 and Phase 2 trial), and include both arterial and venous thrombosis, such as fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, the need for urgent revascularization procedures, gangrene, and thrombosis requiring amputation. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. In addition, new vascular occlusive events have been reported involving the eye, including loss of vision due to blood clots, and occlusion of mesenteric blood vessels. Of note, similar rates of serious vascular events have not been observed in several other drugs of this class. Also, the information available at present indicates that the vascular events are not predictable and are not preventable. The mechanism of action leading to these vascular events is not understood by the FDA or Ariad at this time. Vascular events have occurred at dose levels lower than the 45 mg daily recommended dose.

The Division's assessment has identified a substantially increased vascular toxicity risk with Iclusig (ponatinib) that is different from what was initially described in the initial prescribing information. The Division's assessment indicates a less favorable benefit-to-risk profile for the drug, as compared to that at the time of approval, and for the current indicated treatment population. Therefore DHP, together with the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE), and Office of Translational Sciences (OTS) considered potential risk minimization strategies, including safety labeling changes, changes to limit the indication to a more refractory leukemia population, and a REMS (Risk Evaluation and Mitigation Strategy), to improve the safety profile of Iclusig.

Updated safety information to be incorporated into the prescribing information

1. Revision of the indication to a more refractory patient population.

Iclusig is a kinase inhibitor indicated for the:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

2. Update the Boxed Warning and Warnings and Precautions section with new safety information

The updated sections and the updated content are as follows:

5.1 Vascular Occlusion

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in at least 27% of Iclusig-treated patients from the phase 1 and phase 2 trials. Iclusig can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Iclusig can also cause recurrent or multi-site vascular occlusion.

In the dose-escalation (phase 1) clinical trial, 48% (31/65) of patients with CML or Ph+ ALL developed vascular occlusive events. The median time to onset of the first vascular occlusion event was 5 months. Iclusig can cause fatal and life-threatening vascular occlusion in patients treated at dose levels as low as 15 mg per day.

Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia (see Table 4).

Table 4: Vascular Occlusion Incidence in Iclusig-Treated Patients in the Phase 2 Trial According to Risk Categories

	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia	**No history of ischemia, hypertension, diabetes, or hyperlipidemia**
Age: 49 or younger	18% (6/33)	12% (13/112)
Age: 50 to 74 years	33% (50/152)	18% (20/114)
Age: 75 and older	56% (14/25)	46% (6/13)
All age groups	33% (70/210)	16% (39/239)
Total	24% (109/449)	

Arterial Occlusion and Thrombosis

Arterial thrombosis and occlusion occurred in at least 20% (91/449) of Iclusig-treated patients with some patients experiencing events of more than one type. Patients have required revascularization procedures (cerebrovascular, coronary, and peripheral arterial) due to vascular occlusion from Iclusig.

Cardiac vascular occlusion, including fatal and life-threatening myocardial infarction and coronary artery occlusion has occurred in 12% (55/449) of Iclusig-treated patients, Patients have developed heart failure concurrent or subsequent to the myocardial ischemic event.

Cerebrovascular occlusion, including fatal stroke has occurred in 6% (27/449) of Iclusig-treated patients. Iclusig can cause stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery).

Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease have occurred in 8% (36/449) of Iclusig-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations.

Venous Thromboembolism

Venous thromboembolic events occurred in 5% (23/449) of Iclusig-treated patients, including deep venous thrombosis (8 patients), pulmonary embolism (6 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients).

5.6 Neuropathy

Peripheral and cranial neuropathy have occurred in Iclusig-treated patients. Overall, 13% (59/449) of Iclusig-treated patients experienced a peripheral neuropathy event of any grade (2%, grade 3/4). In clinical trials, the most common peripheral neuropathies reported were peripheral neuropathy (4%, 18/449), paresthesia (4%, 17/449), hypoesthesia (2%, 11/449), and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 1% (6/449) of Iclusig-treated patients (<1% grade 3/4).

Of the patients who developed neuropathy, 31% (20/65) developed neuropathy during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting Iclusig and evaluate if neuropathy is suspected.

5.7 Ocular Toxicity

Serious ocular toxicities leading to blindness or blurred vision have occurred in Iclusig-treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 3% of Iclusig-treated patients. Conjunctival or corneal irritation, dry

eye, or eye pain occurred in 13% of patients. Visual blurring occurred in 6% of the patients. Other ocular toxicities include cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment *[see Adverse Reactions (6)]*.

8.5 Geriatric Use

One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over… Forty-six percent of patients ≥ 65 years had vascular occlusion events.

Institution of a REMS

The REMs will include communication of changes to the prescribing information and safety risks, using a combination of Dear Healthcare Provider letters, email communication, journal advertising, and REMS information webpage to inform prescribers of the revised indications for Iclusig and the serious risks of vascular occlusion associated with treatment. Please see the DRISK review for further information.

Post marketing requirements to further characterize safety and dosing

PMR 1

Propose and conduct an enhanced pharmacovigilance study of data from clinical trials and all postmarketing sources to assess risk factors for, management of, and consequences of all vascular occlusive events that are serious or require medical evaluation or treatment, occurring while patients are receiving ponatinib or within 30 days of the last drug dose.

PMR Schedule Milestones:

Draft Synopsis Protocol Submission:	03/2014
Final Protocol Submission:	06/2014
Study/Trial Completion:	03/2017
Final Report Submission:	12/2017

PMR 2

Conduct a prospective observational study to evaluate the incidence of and risk factors for vascular occlusive events when ponatinib is given with or without anticoagulant or antiplatelet agents. Submit a protocol that includes measures to ensure sufficient long term follow up to adequately capture late occurring vascular occlusive events and describe measures that minimize loss to follow-up.

PMR Schedule Milestones:

Draft Synopsis Protocol Submission:	03/2014
Final Protocol Submission:	10/2014
Study/Trial Completion:	10/2018
Final Report Submission:	06/2019

PMR 3

Provide long-term follow-up of all patients enrolled in the Phase 1 (AP24534-07-101) and Phase 2 (AP24534-10-201) clinical trials. Assess the long-term safety of ponatinib treatment, including the long-term risk of vascular occlusive events. Include narratives for all cases of vascular occlusion. The final report submission should include text and data sets.

PMR Schedule Milestones:

Final Report Submission:	03/2017

PMR 4

Conduct a randomized, multi-arm trial to characterize the safety of a range of ponatinib doses. The trial should be of sufficient size and duration to inform safe use of Iclusig in chronic phase CML. The trial should also assess the efficacy of the doses investigated. Include a plan for adequate PK sampling to provide exposure-toxicity and exposure-response data sufficient to identify appropriate dose ranges (or exposure targets) for patients with T315I mutation and for patients who have progressed after at least two TKIs and are considered to have no alternative therapy available.

PMR Schedule Milestones:

Draft Synopsis Protocol Submission:	04/2014
Final Protocol Submission:	07/2014
Study/Trial Completion:	12/2018
Final Report Submission:	06/2019

PMR 5

Submit the final study report (using a data cut-off of 30 days following the last dose) for the Phase 3 clinical trial, AP24534-12-301 entitled "Phase 3 Randomized, Open-Label Study of Ponatinib vs. Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase." Include narratives for all cases of vascular occlusion. The final report submission should include text and data sets. Include pharmacokinetic exposure-response and dose-response analyses in final report.

PMR Schedule Milestones:

Final Report Submission:	03/2014

PMR 6

Submit integrated safety data and summary (final report submission) from all three clinical trials (Phase 1, Phase 2, and Phase 3). Include narratives for all cases of vascular occlusion.

(b) (4)

PMR Schedule Milestones:

Final Report Submission: 04/2014

T315I mutation testing

The use of a companion diagnostic is not essential for ponatinib treatment because ponatinib is active regardless of T315I mutational status. In clinical practice, testing for the T315I mutation is performed for patients whose disease appears to have resistance to the currently available tyrosine kinase inhibitors. Currently there is not an approved companion diagnostic test for T315I mutation. The following text from the Draft Guidance for Industry and Food and Drug Administration Staff on In Vitro Companion Diagnostic Devices (http://wcms.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf) provides the following guidance on whether a companion diagnostic is necessary: *FDA does not include in this definition clinical laboratory tests intended to provide information that is useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product.*

Therefore the proposed labeling, using a genetic marker, appears to be acceptable and does not require a companion diagnostic for approval.

Conclusions:

- FDA determined the requirement for new safety provisions under the Food and Drug Administration Amendments Act (FDAAA) and notified Ariad of the requirement for revised safety labeling, REMS, and additional post-marketing requirements to further characterize safety and dosing.
- FDA required changes to the Iclusig prescribing information.
- Ariad agreed to limit the indication for ponatinib.
- Ariad agreed on a REMS designed to provide a multi-faceted communication plan to notify prescribers of changes to the prescribing information and safety risks.
- Ariad agreed to conduct additional post marketing investigations to evaluate dose selection, drug exposure, treatment response, and toxicity of therapy.

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/s/

NICOLE C VERDUN
12/19/2013

ROMEO A DE CLARO
12/19/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	203469
	• [redacted] (b) (4)
	• November 27, 2013; SDN 234, SN 085, Prior Approval Labeling Supplement-7
	• December 2, 2013; SDN 236, SN 087, Response to IR (not reviewed)
Brand Name	ICLUSIG®
Generic Name	ponatinib
Indications	treatment of 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
Formulation	15 mg and 45 mg tablets
Dosing Regimen	45 mg once daily
Sponsor	ARIAD Pharmaceuticals, Inc.

1 Executive Summary

The optimal starting dose of Iclusig is unknown. The clinical pharmacology review of the Original NDA (December 5, 2012) recommended that a lower starting dose of ponatinib (< 45 mg daily) could maintain efficacy and reduce the incidence of serious adverse events (AE). Explicit dose recommendations were not given at the time of the Original NDA review due limited exposure data and the expedited review timeline. However, increased incidences of serious AEs seen in ongoing trials and post-marketing, provide an opportunity to reevaluate the dose optimization of ponatinib from risk/benefit standpoint.

Clinical and non-clinical data was evaluated to assess the impact of ponatinib dose, exposure, and/or dose intensity on BCR-ABL suppression, percent pCRKL reduction, efficacy and safety. Pharmacokinetic (PK) data from the first-in-man (FIM) study indicate that the minimally biologically effective dose of ponatinib is likely between 8 and 30 mg, however further clinical study is needed to confirm this finding. For targeted therapies, additional benefit of dosing over target suppression has yet to be determined.

At the time of the Original NDA review, a dose intensity-response[1] relationship was seen for ponatinib and grade ≥ 3 adverse events (e.g., hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression). The focus of the current labeling supplement is on the increased incidence in vascular occlusive event risk. Therefore, the key question was to examine whether a similar relationship exists between dose-intensity and vascular occlusive event risk, such that a lower starting dose can be justified. To assess this, the clinical pharmacology review team requested additional data from the sponsor on November 25, 2013. The sponsor submitted the analysis datasets (with reference to raw datasets) on December 2nd (SDN 236), and was received by the reviewers on December 3rd. In addition to the dose intensity-safety data, the clinical pharmacology review team also requested dose intensity-efficacy data to conduct additional analysis which was also submitted by the

[1] the dose intensity calculation submitted by the sponsor was not deemed to be adequate therefore this dose-intensity relationship will need to be re-evaluated.

sponsor on December 2nd. This request was to assure that a recommendation for a lower starting dose to reduce the vascular occlusive event risk would not have the unintended consequence of also diminishing efficacy at the population level.

Definitive dose intensity-safety and efficacy analyses could not be completed in advance of the Division of Hematology Products (DHP) deadline to send the final label to the sponsor on December 5, 2013. The Office of Clinical Pharmacology, therefore, cannot provide definitive recommendations on the starting dose of ponatinib. Additional analysis based on the data recently submitted by the sponsor to identify the safe and effective starting dose need to be conducted before definitively making recommendations. (b) (5) (b) (5).

1.1 Recommendations

The Office of Clinical Pharmacology is unable to recommend a safe and effective starting dose for patients at this time. Based on dose intensity-response analysis (conducted as part of the original review), biological activity assessment (BCR-ABL and pCRKL) and plasma levels achieved in patients, a starting dose lower than 45 mg may offer a better benefit-risk profile. Based on the recently submitted data further evaluation of optimal dosing strategies is ongoing and will be completed.

1.2 Post Marketing Requirements

A post marketing requirement for dose is still under discussion. On November 24, 2013 the following PMR was communicated to the sponsor by DHP:

> 3. A randomized, multi-arm trial to characterize the safety of a range of ponatinib doses. The trial should be of sufficient size and duration to inform safe use of Iclusig in chronic phase CML. The trial should also assess the efficacy of the doses investigated. Include a plan for adequate PK sampling to provide exposure-toxicity and exposure-response data sufficient to identify appropriate dose ranges (or exposure targets) for patients with T315I mutation and for patients who have progressed after at least two TKIs and are considered to have no alternative therapy available.

The Office of Clinical Pharmacology should be a part of the discussion of the study design of a dose-finding PMR. In addition, the PK, efficacy and safety data from the phase 3 trial (AP24534-12-301, EPIC study) of 45 mg QD ponatinib vs. 400 mg QD imatinib should be reviewed prior to justifying the doses for an a dose-optimization PMR.

1.3 Signatures

Julie M. Bullock, Pharm.D. Team Leader Division of Clinical Pharmacology V	Nitin Mehrotra, Ph.D. Team Leader Division of Pharmacometrics
Nam Atiqur Rahman, Ph.D. Division Director Division of Clinical Pharmacology V	Vikram Sinha, Ph.D. Director Division of Pharmacometrics

Cc:

DHP:	Deputy Director for Safety – **R Kane**; Medical Officer – **N Verdun**; Medical TL – **A DeClaro**
DCPV:	TL - **J Bullock**; DDD - **B Booth**; DD - **A Rahman**
DPM:	TL – **N Mehrotra**, DD – **V Sinha**
OCP:	Office Director: **I Zineh**

2 Background

ICLUSIG (ponatinib) is an orally administered tyrosine kinase inhibitor (TKI) that primarily targets BCR-ABL (including the BCR-ABL T315I mutant). ICLUSIG received accelerated approval on December 14, 2012 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
- Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. This indication is based upon response rate.

There are no trials verifying an improvement in disease-related symptoms or increased survival with ICLUSIG.

ICLUSIG was reviewed under a 'breakthrough' time line in less than 6 months. At the time of approval there was an ongoing confirmatory phase 3 trial (AP24534-12-301, EPIC study) of 45 mg QD ponatinib vs. 400 mg QD imatinib in patients with newly diagnosed CP-CML.

(b) (4)

On October 8, 2013 all Phase 1 and Phase 2 trials under IND 78375 were placed on partial clinical hold (no enrollment of new patients). Findings from review of the safety data resulted in a Drug Safety Communication on October 11, 2013. On October 18, 2013 the ongoing phase 3 trial (AP24534-12-301, EPIC) in newly diagnosed CP-CML was terminated. A request for temporary suspension of marketing was issued by the FDA on November 1, 2013. On November 1, 2013 Ariad agreed to suspend marketing of ICLUSIG in the United States (SDN 226).

Relevant Clinical Pharmacology Findings from Original NDA Approval

At the time of approval the major safety issues identified by the medical officer included: arterial thromboembolic events (i.e., myocardial infarction, stroke, peripheral arterial disease), arterial stenosis, hepatic toxicity, myelosuppression, hemorrhage, pancreatitis, hypertension, congestive heart failure, supraventricular tachyarrhythmias (i.e., atrial fibrillation, atrial flutter, atrial tachycardia, supraventricular tachycardia), cardiac conduction defects including QTc prolongation, venous thromboembolism, tumor lysis syndrome, gastrointestinal perforation, compromised wound healing, and fluid retention.

The clinical pharmacology review concluded that the proposed 45 mg QD dose is not supported by the dose intensity-response relationship for efficacy and safety and that a lower dose may offer a better benefit-risk profile. It should also be noted that 75% of patients enrolled in the pivotal trial (AP24534-10-201) had their dose reduced due to adverse events; forty nine percent of patients required dose reduction to 30 mg while 25% of patients required dose reduction to 15 mg.

Since the pivotal trial (AP24534-10-201) did not include sparse sampling, an optimal dose, dose schedule or exposure of ponatinib could not be identified. A post marketing requirement (PMR 1984-1) for collection of additional PK sampling in the ongoing phase 3 trial (AP24534-12-301)

was issued to provide the needed information to support future exploration of an optimal dose. In addition, a PMR (1984-6) to evaluate the in vitro potential for the displacement of ponatinib from its protein binding sites in human plasma following addition of frequently used, highly protein-bound co-medications was agreed upon and the report should be submitted in March of 2014. PMR 1984-6 is relevant to the vascular occlusive safety signal as many patients with cardiovascular and ischemic events may take drugs such as aspirin, digoxin, nifedipine, propranolol, and warfarin.

Increased Safety Concerns

The cardiovascular safety profile for ICLUSIG continues to be notable for arterial ischemic and thrombotic occlusive events, hypertension and hepatotoxicity. The rate of vascular occlusive events in trial AP24534-10-201 (still ongoing for long-term safety follow-up) has now increased to 24%.[2]

- Cardiac vascular occlusion, including fatal and life-threatening myocardial infarction and coronary artery occlusion has occurred in 12% (55/449) of Iclusig-treated patients.
- Cerebrovascular occlusion, including fatal stroke has occurred in 6% (27/449) of Iclusig-treated patients.
- Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease have occurred in 8% (36/449) of Iclusig-treated patients.

Through the review of both the Original NDA and the current submissions the investigator and Sponsor's designation of seriousness and CTCAE grading of these vascular occlusive events may not have adequately capture the severity of the safety issue. The clinical team noted several Grade 2 to 4 vascular occlusive events (e.g., Grade 3 extremity necrosis, Grade 3 peripheral arterial disease, Grade 2 vertebral artery stenosis) have not been categorized as serious adverse events. Further, timely reporting is suspect. The event rates are believed to underestimate the true risks of ponatinib.

Optimal Starting Dose

In light of the increasing cardiovascular safety reports, the adequacy of the ponatinib dose has been questioned. In the first-in-man phase 1 dose escalation study (AP24534-07-101) doses of 2, 4, 8, 15, 30, 45 and 60 mg QD were studied in patients with refractory or advanced hematologic malignancies. Overall, 65 patients had Ph+ leukemia (60 CML (43 CP-CML, 9 AP-CML and 8 BP-CML) and 5 Ph+ALL). In addition to CML, 12 patients had AML and 4 patients had other hematologic malignancies.

Four dose limiting toxicities (DLTs) were observed in 11 patients at the 60 mg dose. One DLT was observed in 12 patients at the 45 mg dose. The sponsor's justification of the 45 mg dose was based on acceptable toxicity and anti-leukemic activity (responses were highest in patients treated with 45 mg ponatinib) even though responses (and activity) were seen at doses as low as 8 mg. Biologic activity (inhibition of phosphorylation of CRKL and concentrations needed to sufficiently suppress BCR-ABL mutant clones) of ponatinib was seen at doses less than 45 mg (see Appendix 4.1).

[2] percentages from prescribing information to be sent to sponsor on December 4, 2013

Dose Intensity analyses

There were several interactions between the sponsor and the Agency to understand the methodology the sponsor was following to calculate dose intensity. The sponsor was asked to submit datasets/reports to clearly explain their methodology and to calculate the dose-intensity analysis several different ways to conduct additional sensitivity analysis for dose intensity-safety relationships. It was noticed by the Clinical Pharmacology review team that when sponsor submitted the datasets, there were still some discrepancies regarding the calculation for dose-intensity.

Therefore, a detailed information request (IR) was submitted to the sponsor on November 25, 2013 to clarify those discrepancies and to also to submit additional datasets (including raw datasets) for further FDA analysis. The sponsor submitted the data, per the IR on December 2nd, 2013. This data is still under review.

3 Labeling

Only relevant sections pertaining to clinical pharmacology are included below.

3.1 FDA labeling to be sent to sponsor on December 4, 2013

2.1 Recommended Dosing

The optimal dose of Iclusig has not been identified. In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.

Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for CP CML and AP CML patients who have achieved a major cytogenetic response.

Iclusig may be taken with or without food. Tablets should be swallowed whole.

12.2 Pharmacodynamics

In a cell-based assay, ponatinib concentrations of 20 nM (10.65 ng/mL) were sufficient to suppress most BCR-ABL mutant clones. However, ponatinib concentrations of 40 nM (21.3 ng/mL) were required to suppress T315I mutants. The median and range of steady-state C_{max} and trough (C_{min}) concentrations of ponatinib following 29 days of once-daily dosing of 15 mg, 30 mg and 45 mg are listed in Table 9.

Table 9: Median, Maximum, and Minimum Ponatinib Exposure at Steady-State by Dose Group: PK Evaluable Population

Dose	Median C_{max} (Range) (nM)	Median C_{min} (Range) (nM)
15 mg QD (n = 8)	49 (23 – 105)	28 (11 – 68)
30 mg QD (n = 9)	125 (67 – 178)	54 (41 – 89)
45 mg QD (n = 21)	161 (64 – 336)	67 (22 – 137)

Concentrations of ponatinib shown in cell-based assays to suppress unmutated BCR-ABL and most mutant BCR-ABL clones may be achieved at once daily dosing of 15 mg or 30 mg.

The dose intensity-safety relationship indicated that there are significant increases in grade ≥ 3 adverse events (hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) over the dose range of 15 to 45 mg once-daily.

3.2 History of Sponsor's proposed labeling for Section 2.1 - Recommended Dosing

11/27/13 Sponsor's proposed labeling (SDN234/SN085)

2.1 Recommended Dosing

The optimal dose of Iclusig has not been identified. In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.

Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for CP CML and AP CML patients who have achieved a major cytogenetic response.

Iclusig may be taken with or without food. Tablets should be swallowed whole.

10/22/13 Sponsor's proposed labeling (SDN216/SN073)

2.1 Recommended Dosing

(b) (4)

10/15/13 Sponsor's proposed labeling (SDN 210/SN 071)

2.1 Recommended Dosing

(b) (4)

Iclusig may be taken with or without food. Tablets should be swallowed whole.

9/17/13 Sponsor's proposed labeling (SDN188/SN061)

2.1 Recommended Dosing

(b) (4)

Iclusig may be taken with or without food. Tablets should be swallowed whole.

8/30/13 Sponsor's proposed labeling (SDN172/SN060)

2.1 Recommended Dosing

(b) (4)

Iclusig may be taken with or without food. Tablets should be swallowed whole.

4 Appendix

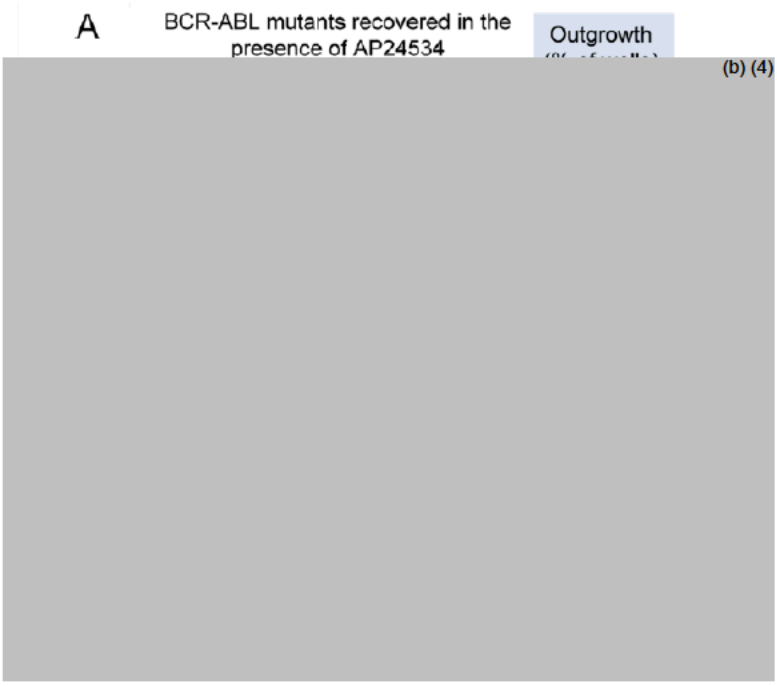
4.1 In vitro IC_{100} and FIM PK/PD

Suppression of BCR-ABL mutant clones

A plasma ponatinib concentration of 40 nM (21.3 ng/mL) represented exposures sufficient to suppress the emergence of any BCR-ABL mutant clones (see Figure 1 below excerpted from the pharmacology/toxiciology review of the original NDA), including T315I, in a preclinical mutagenesis assay. Ponatinib concentrations of 20 nM ((b) (4) ng/mL) were sufficient to suppress the majority of BCR-ABL mutant clones except T315I and E255V.

Figure 1 Frequency and Scope of BCR-ABL mutants recovered after AP24534 treatment

(Excerpted from the Applicant's Submission)



In the first-in-man phase 1 dose escalation study (AP24534-07-101) at steady state (Day 29) the median Cmin was 20 nM following ponatinib 8 mg QD and > 40 nM following ponatinib 30 mg QD (see Table 1). This suggests that a daily dose of 30 mg is more than sufficient to continually suppress 100% of BCR-ABL mutants. Concentrations of ponatinib greater than 40 nM would not necessarily increase the activity of ponatinib, but could stimulate off target kinases and potentially lead to greater toxicity. Further, since concentrations of 20 nM were sufficient to suppress the majority of BCR-ABL mutant clones except T315I and E255V, this suggests that patients who do not express T31KI mutant BCR-ABL may be treated effectively with a ponatinib dose lower than 30 mg (see Figure 1)

Table 1. Day 29 median (range) Cmax and Cmin ponatinib concentrations*

Dose	Cmax (uM)	Cmin (uM)
8 mg QD (n = 6)	29 (16 – 33)	20 (11 – 26)
15 mg QD (n = 8)	49 (23 – 105)	28 (11 – 68)
30 mg QD (n = 9)	125 (67 – 178)	54 (41 – 89)
45 mg QD (n = 21)	161 (64 – 336)	67 (22 – 137)

*converted from ng/mL to uM from sponsors CSR AP24534-07-101 table 11-24 using molecular weight of 532.56 g/mol

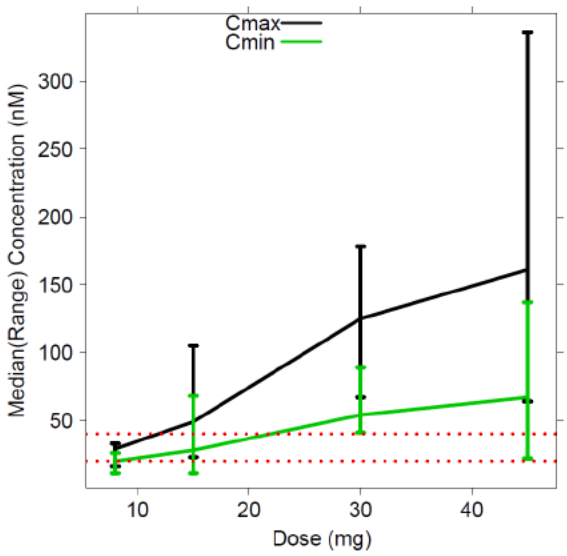


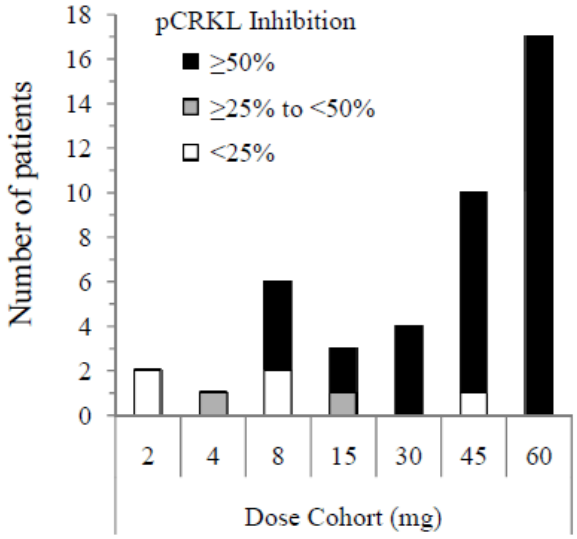
Figure 1. Median (range) ponatinib concentrations following 29 daily doses of ponatinib 8 to 45 mg. The red dotted lines demarcate the 20 nM and 40 nM thresholds for in vitro activity.

Phosphorylation of the BCR-ABL Substrate CRKL

It is established from experience with imatinib, dasatinib and nilotinib that reduction in levels of phosphorylation of the BCR-ABL substrate CRKL (pCRKL) by at least 50% in the first cycle is associated with clinical response and that elevated pCRKL levels has been associated with acquired resistance to therapy.[3]

[3] White D, Saunders V, Grigg A, Arthur C, Filshie R, Leahy MF, et al. Measurement of in vivo BCR-ABL kinase inhibition to monitor imatinib-induced target blockade and predict response in chronic myeloid leukemia. J Clin Oncol. 2007;25(28):4445-51

Figure 11 Summary of Pharmacodynamic Data in Phase 1 Clinical Trial AP24534-07-101



A reduction in pCRKL by ≥ 50% was observed in 67% of patients receiving 8 mg of ponatinib (see Figure 11 above). The two patients who did not achieve a ≥ 50% reduction in pCRKL in the 8 mg dose cohort were positive for T315I mutant BCR-ABL. Based about what we know from the preclinical mutagenesis assay the two patients with T315I mutations in the 8 mg cohort would have needed to have concentrations close to 40 nM to suppress T315I. Following 8 mg the range of Cmin concentrations was limited to 11 to 26 nM which indicates that patients with T315I would need doses > 8 mg to achieve these 40 nM concentrations. At doses ≥ 15 mg the majority of patients demonstrated a ≥ 50% reduction in pCRKL in patients both with or without T315I mutations.

The information regarding pCRKL reduction and BCR-ABL suppression should be included in labeling (See Section 3).

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/s/

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12/04/2013

NITIN MEHROTRA
12/04/2013

NAM ATIQUR RAHMAN
12/04/2013

VIKRAM P SINHA
12/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
Division of Hematology Products (DHP)

Application: 203469/S-007 and S-008

Name of Drug: Iclusig® (ponatinib) 15 mg and 45 mg tablets for oral use

Applicant: ARIAD Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: November 27, 2013

Receipt Date: November 27, 2013

Background and Summary Description:
Iclusig is a tyrosine kinase inhibitor that was originally approved on December 14, 2012 under Accelerated Approval 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. At the time of the initial approval, the label contained information about the risks of blood clots in the Boxed Warning and Warnings and Precautions sections of the Full Prescribing Information.

Post approval, the Agency became aware of new clinical trial data, as well as postmarketing safety reports indicating an increase of arterial and venous occlusions in patients treated with Iclusig. The Agency considered this to be "new safety information" as defined under the Federal Food, Drug, and Cosmetic Act (FDCA) and acted accordingly. The Agency issued Drug Safety Communications (DSC) on October 11 and October 31, 2013 to convey this new safety finding of the increased risk of occlusive events. Marketing of the drug Iclusig was voluntarily suspended by Ariad Pharmaceuticals on October 31, 2013 and the Agency issued a third DSC on November 5, 2013 to inform physicians and patients of an expedited process for obtaining the drug under emergency IND.

On November 25, 2013, the Agency issued a formal communication the provided for safety labeling change requirement, the need for a REMS, and the need for additional postmarketing requirement studies. Following this communication, the Agency held a Tcon with Ariad on November 26, 2013 to discuss what elements need to be submitted in accordance with the November 25, 2013 letter. That discussion pertained to the REMS, post marketing requirement studies (PMRs), and revisions to the label based on the new safety data.

In response, Ariad submitted a labeling supplement (S-0 7) on November 27, 2013 and a REMS supplement (S-008) on December 5, 2013.

This supplemental application proposes the inclusion of new safety information in the Iclusig labeling, specifically an increase in frequency of vascular occlusions. In addition, the indication has been limited to a more refractory patient population.

These labeling changes, together with the implementation of a REMS and post marketing requirement studies/trials are needed in order to resume marketing of Iclusig.

The following sections of the US Prescribing Information (PI) have been revised:

- BOXED WARNING
- Section 1 INDICATIONS AND USAGE,
- Section 2 DOSAGE AND ADMINISTRATION
- Section 5 WARNINGS AND PRECAUTIONS
- Section 6 ADVERSE REACTIONS
- Section 7 DRUG INTERATCTIONS
- Section 8 USE IN SPECIFIC POPULATIONS
- Section 12 CLINICAL PHARMACOLOGY
- Section 14 CLINICAL STUDIES
- Section 17 PATIENT COUNSELING INFORMATION

Review

This review is based on the applicant's submitted Adobe format of the PI. The proposed PI was compared to the current approved PI (12/14/12) to ensure all changes were shown as track changes to allow for an appropriate review of the PI. The following changes have been identified and are indicated as follows: Deletions are shown as ~~strikeouts~~ and additions are shown as <u>double underlines</u>. The following revisions were noted.

The team met and reviewed the labeling on November 29, 2013 and December 2, 2013. The revisions made to the labeling were based on the Division's Safety and Clinical teams' review of the data. DHP's review identified substantial differences in safety outcomes since the time of approval. FDA's analysis also noted differences in adverse event severity.

The changes described in this review are the agreed-upon revisions to the PI.

Highlights of Prescribing Information

The changes identified below are specific to the Highlights.

1. The Boxed Warning has been revised to include the new safety information.

WARNING: ~~ARTERIAL THROMBOSIS~~ VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY

~~**Arterial Thrombosis:**~~

- ~~**Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke have occurred in Iclusig-treated patients. In clinical trials, serious arterial thrombosis occurred in 8% of Iclusig-treated patients. Interrupt and consider discontinuation of Iclusig in patients who develop arterial thrombotic events *(2.3) (5.1)*.**~~

~~**Hepatotoxicity:**~~

- **Vascular Occlusion: Arterial and venous thrombosis and occlusions have occurred in at least 27% of Iclusig treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion. (5.1).**
- **Heart Failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure (5.2).**
- **Hepatotoxicity, liver failure, and death have occurred in Iclusig-treated patients. Monitor hepatic function ~~prior to and during treatment.~~ Interrupt ~~and then reduce or discontine~~ Iclusig ~~for~~ if hepatotoxicity is suspected (2.3, 5.~~2~~4).**

2. The Recent Major Changes of the Highlights were updated to incorporate the new safety information and relevant revisions to the Prescribing Information.

RECENT MAJOR CHANGES:	
Boxed Warning	12/2013
Indications and Usage (1)	12/2013
Dosage and Administration (2)	12/2013
Warnings and Precautions, (5.1, 5.2, 5.4, 5.6, and 5.7)	12/2013

3. The Indication statement was revised and limited to a more refractory leukemia population as a result of the FDA's comprehensive safety evaluation. This change is reflected in both the Highlights and the Full Prescribing Information.

INDICATIONS AND USAGE:

Iclusig is a kinase inhibitor indicated for the ~~treatment:~~

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase ~~chronic myeloid leukemia (CML) that is resistant~~) or ~~intolerant to prior tyrosine kinase inhibitor therapy or~~T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) ~~that is resistant).~~

- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or ~~intolerant to prior~~ Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated. (1~~)~~

~~This indication is~~ These indications are based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

4. Under the Highlights, the Warnings and Precautions were revised and updated to incorporate the new safety information.

WARNINGS AND PRECAUTIONS

~~• Congestive Heart Failure: Monitor patients for signs or symptoms of congestive heart failure and treat as clinically indicated (5.3, 6).~~
- Hypertension: Monitor for high blood pressure and ~~treat~~ manage as clinically indicated (5.4, 6).
- Neuropathy: (5.6, 6) Monitor for symptoms of peripheral and cranial neuropathy.
- Ocular Toxicity: Conduct comprehensive eye exams at baseline and periodically during treatment (5.7).
- Hemorrhage: Interrupt Iclusig for serious or severe hemorrhage (5 ~~6~~.8, 6).
- Fluid Retention: Monitor patients for fluid retention; interrupt, reduce, or discontinue Iclusig (5.~~7~~ 9, 6).
- Cardiac Arrhythmias: Monitor for symptoms of arrhythmias (5.~~8~~ 10, 6).
- Myelosuppression: Thrombocytopenia, neutropenia, and anemia may require dose interruption or reduction. Monitor complete blood counts every 2 weeks for 3 months and then monthly and as clinically indicated. Interrupt Iclusig for ANC < 1000/mm^3 or thrombocytopenia < 50,000/ mm^3 (2.2, 5. ~~9~~ 11, 6).
- Tumor Lysis Syndrome: Ensure adequate hydration and correct elevated uric acid levels prior to initiating therapy with Iclusig (5.~~10~~12).
- Compromised Wound Healing and Gastrointestinal Perforation: Temporarily interrupt therapy in patients undergoing major surgical procedures (5.~~11~~13).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of potential risk to a fetus (5.~~12~~14, 8.1).

Revised: **~~[12/2012]~~** [12/2013]

Table of Contents (TOC)

1. The TOC was updated to reflect the changes made in the Full Prescribing Information. Specifically, the Boxed Warning, Section 5 - Warnings and Precautions, and Section 12 – Clinical Pharmacology.

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ~~ARTERIAL THROMBOSIS~~ VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY

5 WARNINGS AND PRECAUTIONS
~~5.1 Thrombosis and Thromboembolism~~
5.1 Vascular Occlusion
5.2 Heart Failure
5.3 Hepatotoxicity
~~5.3 Congestive Heart Failure~~
5.4 Hypertension
5.5 Pancreatitis
5.6 Neuropathy
5.7 Ocular Toxicity
5.8 Hemorrhage
5.~~7~~9 Fluid Retention
5.~~8~~10 Cardiac Arrhythmias
5.~~9~~11 Myelosuppression
5.~~10 Tumor~~ 12Tumor Lysis Syndrome
5.~~11~~13 Compromised Wound Healing and Gastrointestinal Perforation
5.~~12~~14 Embryo-Fetal Toxicity

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics

Full Prescribing Information

The changes described below are specific to the Full Prescribing Information (FPI).

1. Based upon FDA's safety analysis, the Boxed Warning was revised to reflect the serious risk of vascular occlusive events, including arterial and venous thrombosis events. Furthermore, heart failure was also added to the Boxed Warning, as the safety review identified cases of myocardial infarction.

WARNING: ~~ARTERIAL THROMBOSIS~~VASCULAR OCCLUSION, HEART FAILURE,

and HEPATOTOXICITY

Vascular Occlusion:

- **Arterial ~~Thrombosis: Cardiovascular, cerebrovascular,~~ and ~~peripheral vascular~~ venous thrombosis and occlusions have occurred in at least 27% of Iclusig treated patients, including fatal myocardial infarction ~~and~~, stroke ~~have occurred in Iclusig treated patients. In clinical trials, serious~~ stenosis of large arterial ~~thrombosis occurred in 8% of Iclusig-treated patients. Interrupt and consider discontinuation of Iclusig in patients who develop arterial thrombotic events *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*~~vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events (5.1).**
- **Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion. A benefit-risk consideration should guide a decision to restart Iclusig therapy (5.1).**

Heart Failure:

- **Heart failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure (5.2).**

Hepatotoxicity:

- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function ~~prior to and during treatment~~. Interrupt ~~and then reduce or discontinue~~ Iclusig ~~for~~ if hepatotoxicity *~~[see Dosage and Administration~~* is suspected *~~(~~(2.3) ~~and Warnings and Precautions, 5.2)]~~3)*.**

2. Under Section 1, Indications and Usage, in the FPI, the clinical and safety team revised the indication to limit its use to a more specific patient population.

1 INDICATIONS AND USAGE

Iclusig® (ponatinib) is a kinase inhibitor indicated for the ~~treatment~~:

Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase ~~chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or))~~ and T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) ~~that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.)~~.

~~This indication is*~~Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

These indications are based upon response rate *[see Clinical Studies (14)]*. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

3. Under Section 2, Dosage and Administration, the language was revised by the clinical and clinical pharmacology review teams to state that an optimal dose has not yet been identified. Additional information regarding dose reduction was added.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The ~~recommended~~optimal dose ~~and schedule for~~ of Iclusig ~~is~~ has not been identified. In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. ~~Continue treatment as long as the patient does not show evidence of diease progression~~However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.
Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for CP CML and AP CML patients who have achieved a major cytogenetic response.
Consider discontinuing Iclusig if response has not occurred by 3 months (90 days).

2.3 Dose Modifications for Non-Hematologic Adverse Reactions

If serious non-hematologic adverse reaction occurs, modify the dose or interrupt treatment. Do not restart Iclusig in patients with ~~serious ischemic~~ arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent ~~ischemia~~ arterial or venous occlusions and the patient has no other treatment options. For serious reactions other than ~~ischemia~~ arterial or venous occlusion, do not restart Iclusig until the serious event has resolved or the potential benefit of resuming therapy is judged to outweigh the risk.

4. Under Section 5, Warnings and Precautions, of the FPI has been updated by the Division's Clinical and Safety teams to include the increased risk of vascular occlusion seen with Iclusig (ponatinib). Heart Failure (Section 5.2), Neuropathy (Section 5.4), and Ocular Toxicity (Section 5.7) were also added as sub-sections under Section 5. These changes reflect the FDA's review of the additional safety information and confirm the toxicity is different from what was initially described in the original approval of Iclusig.

Based upon the review of the data, the clinical team also suggested updates to Hepatotoxicity (Section 5.3), Hypertension (Section 5.4), Hemorrhage (Section 5.8), and Cardiac Arrhythmias (Section 5.10).

Lastly, sub-sections under Warnings and Precautions were re-numbered in order to reflect the newly created sub-sections and to align the order in decreasing clinical significance.

5 WARNINGS AND PRECAUTIONS

~~**5.1 Thrombosis and Thromboembolism**~~

5.1 Vascular Occlusion

Arterial ~~Thrombosis~~

~~Cardiovascular, cerebrovascular, and peripheral vascular~~ and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and ~~stroke~~ the need for urgent revascularization procedures have occurred in at least 27% of Iclusig-treated patients from the phase 1 and phase 2 trials. In the dose-escalation clinical trial, 48% (31/65) of patients with CML or Ph+ ALL developed vascular occlusive events. (b) (4)

~~Serious arterial~~Iclusig can cause fatal and life-threatening vascular occlusion (b) (4)

Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia (see Table 4).

Table 4: Vascular Occlusion Incidence in Iclusig-Treated Patients in Phase 2 Trial According to Risk Categories

	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia	**No history of ischemia, hypertension, diabetes, or hyperlipidemia**
Age: 49 or younger	18% (6/33)	12% (13/112)
Age: 50 to 74 years	33% (50/152)	18% (20/114)

	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia	**No history of ischemia, hypertension, diabetes, or hyperlipidemia**
Age: 75 and older	56% (14/25)	46% (6/13)
All age groups	33% (70/210)	16% (39/239)
Total	24% (109/449)	

Arterial Occlusion and Thrombosis

Arterial occlusion and thrombosis occurred in ~~8% (34~~ at least 20% (91/449) of Iclusig-treated patients ~~Twenty~~ with some patients experiencing events of more than one ~~patients~~ type. Patients have required ~~a~~ revascularization ~~procedure (16 patients with~~ procedures (cerebrovascular, coronary, ~~revascularization, 4 patients with,~~ and peripheral arterial ~~revascularization, and 1 patient with cerebrovascular revascularization). Overall, fifty one patients (11%) experienced an arterial thrombosis event of any grade.)~~ due to vascular occlusion from Iclusig.

~~Myocardial~~ Cardiac vascular occlusion, including fatal and life-threatening myocardial infarction ~~or worsening~~ and coronary artery ~~disease was the most common arterial thrombosis event and~~ occlusion has occurred in ~~21 patients (5%)~~ 12% (55/449) of Iclusig-treated patients ~~.Eleven of these patients~~, Patients have developed ~~congestive~~ heart failure concurrent or subsequent to the myocardial ischemic event.

~~Serious cerebrovascular events were reported~~ Cerebrovascular occlusion, including fatal stroke has occurred in ~~2%(8~~6% (27/449) of Iclusig-treated patients. ~~Two patients experienced hemorrhagic conversion of the initial ischemic events. Four patients developed~~ Iclusig can cause stenosis ~~of large~~ over multiple segments in major arterial vessels ~~of~~ that supply the brain (e.g., carotid, vertebral, middle cerebral artery).

(b) (4) Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial ~~events were reported~~ disease have occurred in ~~2% (7~~8% (36/449) of Iclusig-treated patients. ~~Three patients~~ Patients have developed digital or distal extremity necrosis~~;2 of these patients had diabetes mellitus and peripheral arterial disease and~~ and have required amputations.

~~Thirty~~ Clinicians should consider whether the benefits of ~~34~~ Iclusig ~~treated~~ treatment are expected to exceed the risks of therapy. In patients ~~who experienced a serious arterial thrombosis event had one or more cardiovascular risk factors (e.g., myocardial infarction,~~

~~coronary artery disease, angina, stroke, transient ischemic attack, hypertension, diabetes mellitus, hyperlipidemia, and smoking). Patients with cardiovascular risk factors are at increased risk for arterial thrombosis with Iclusig. Interrupt and consider discontinuation of Iclusig in patients who develop~~suspected of developing arterial thrombotic events, interrupt or stop Iclusig. A benefit-risk consideration should guide a decision to restart Iclusig therapy. *[see Dosage and Administration (2.3)]*.

Venous Thromboembolism

Venous thromboembolic events occurred in ~~3%~~ 5% (23/449) of Iclusig-treated patients, including deep venous thrombosis (~~9~~8 patients), pulmonary embolism embolism (~~4~~6 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients). Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism *[see Dosage and Administration (2.3)]*.

5.2 Heart Failure

Fatal and serious heart failure or left ventricular dysfunction occurred in 5% of Iclusig-treated patients (N =22).Eight percent of patients (N= 35) experienced any grade of heart failure or left ventricular dysfunction. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of Iclusig. Consider discontinuation of Iclusig in patients who develop serious heart failure *[see Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

~~Hepatotoxicity that has resulted in~~ Iclusig can cause hepatotoxicity, including liver failure and death ~~occurred in Iclusig treated patients.~~ Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with BP-CML or Ph+ ALL. Severe hepatotoxicity occurred in all disease cohorts.

The incidence of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation was 56% (all grades) and 8% (grade 3 or 4). Iclusig treatment may result in elevation in ALT, AST, or both. ALT or AST elevation was not reversed by the date of last follow-up in 5% of patients.

Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue Iclusig as clinically indicated *[see Dosage and Administration (2.3)]*.

~~**5.3 Congestive Heart Failure**~~

~~Twenty patients treated with Iclusig (4%) experienced serious congestive heart failure or left ventricular dysfunction, with 4 fatalities. Thirty-three patients treated with Iclusig (7%) experienced any grade of congestive heart failure or left ventricular dysfunction. Monitor patients for signs or symptoms consistent with congestive heart failure and treat~~

~~as clinically indicated, including interruption of Iclusig. Consider discontinuation of Iclusig in patients who develop serious congestive heart failure *[see Dosage and Administration (2.3)]*.~~

5.4 Hypertension

Treatment-emergent hypertension occurred in 67% of patients (300/449). Eight patients (2%) treated with Iclusig ~~(2%)~~ in clinical trials experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis. ~~These patients required~~ Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath

~~Treatment-emergent hypertension occurred in 67% of patients (300/449)~~ *[see Adverse Reactions (6)]*. In patients with baseline systolic BP<140 mm Hg and baseline diastolic BP<90mm Hg, 78% (220/282) experienced treatment-emergent hypertension; 49% (139/282) developed Stage 1 hypertension (defined as systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) while 29% developed Stage 2 hypertension (defined as systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg. In 131 patients with Stage 1 hypertension at baseline, 61% (80/131) developed Stage 2 hypertension. Monitor and manage blood pressure elevations during Iclusig use and treat hypertension to normalize blood pressure. Interrupt, dose reduce, or stop Iclusig if hypertension is not medically controlled.

Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue Iclusig as clinically indicated *[see Dosage and Administration (2.3)]*.

5.6 Neuropathy

Peripheral and cranial neuropathy have occurred in Iclusig-treated patients. Overall, 13% (59/449) of Iclusig-treated patients experienced a peripheral neuropathy event of any grade (2%, grade 3/4). In clinical trials, the most common peripheral neuropathies reported were peripheral neuropathy (4%, 18/449), paresthesia (4%, 17/449), hypoesthesia (2%, 11/449), and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 1% (6/449) of Iclusig-treated patients (<1% grade 3/4).

Of the patients who developed neuropathy, 31% (20/65) developed neuropathy during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting Iclusig and evaluate if neuropathy is suspected.

5.7 Ocular Toxicity

Serious ocular toxicities leading to blindness or blurred vision have occurred in Iclusig-treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 3% of Iclusig-treated patients. Conjunctival or corneal irritation, dry eye, or eye pain occurred in 13% of patients. Visual blurring occurred in 6% of the patients. Other ocular toxicities include cataracts, glaucoma, iritis,

iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment *[see Adverse Reactions (6)]*.

5.8 Hemorrhage

Serious bleeding events, including fatalities, occurred in 5% (22/449) of patients treated with Iclusig ~~including fatalities Hemorrhagic events.~~ Hemorrhage occurred in 24% of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Cerebral hemorrhage and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia *[see Warnings and Precautions (5.~~9~~11)]*. Interrupt Iclusig for serious or severe hemorrhage and evaluate *[see Dosage and Administration (2.3)]*.

5.~~7~~9 Fluid Retention

5.~~8~~10 Cardiac Arrhythmias

Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 1% (3/449) of Iclusig-treated patients. The cardiac rhythms (1 case each) identified were complete heart block, sick sinus syndrome, and atrial fibrillation with bradycardia and pauses. Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness, or chest pain). Interrupt Iclusig and evaluate.

Supraventricular tachyarrhythmias occurred in 5% (25 ~~(5%)~~/449) of Iclusig-treated patients. Atrial fibrillation was the most common supraventricular tachyarrhythmia and occurred in 20 patients. The other supraventricular tachyarrhythmias were atrial flutter (4 patients), supraventricular tachycardia (4 patients), and atrial tachycardia (1 patient). For 13 patients, the event led to hospitalization. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness). Interrupt Iclusig and evaluate.

5.~~9~~11 Myelosuppression

5.~~10~~12 Tumor Lysis Syndrome

5.~~11~~13 Compromised Wound Healing and Gastrointestinal Perforation

5.~~12~~14 Embryo-Fetal Toxicity

5. Section 6, Adverse Events, of the FPI has been modified to incorporate the changes previously identified under Indication and Usage, Dosage and Administration, and Warnings and Precautions. The changes to this section are based upon the clinical and statistical analysis of the safety data.

Specifically, Table 5 and Table 6 were updated with the new serious adverse event (SAE) information and the criteria used for assessment of the SAEs. The remaining tables in this section have also been renumbered.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- ~~Thrombosis and Thromboembolism~~ Vascular Occlusion *[see Warnings and Precautions (5.1)]*
- ~~Hepatotoxicity~~Heart Failure *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2) ~~and Dosage and Administration (2.3)~~]* ~~]~~
- ~~Congestive Heart Failure~~ Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Pancreatitis *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*
- Neuropathy *[see Warnings and Precautions (5.6)]*
- Ocular Toxicity *[see Warnings and Precautions (5.7)]*
- Hemorrhage *[see Warnings and Precautions (5.~~6~~8)]*
- Fluid Retention *[see Warnings and Precautions (5.~~7~~9)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.~~8~~10)]*
- Myelosuppression *[see Dosage and Administration (2.2) and Warnings and Precautions (5.~~9~~11)]*

The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. All patients received a starting dose of 45 mg Iclusig once daily. At the time of analysis, the median duration of treatment with Iclusig was 337 days in patients with CP-CML, 362 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ ALL. The median dose intensity was 37 mg or , ~~83% of the expected 45 mg dose~~ 83% of the expected 45 mg dose. The events of arterial ischemia, cardiac failure, and peripheral neuropathy reported in Tables 5 and 6 below include data from an additional 13 months of follow-up (median duration of treatment CP-CML: 672 days, AP-CML: 590 days, BP-CML: 89 days, Ph+ ALL: 81 days).

Adverse reactions reported in more than 10% of all patients treated with Iclusig in this trial are presented in Table ~~4~~5. Overall, the most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin,

constipation, arthralgia, nausea, and pyrexia.

The rates of treatment-emergent adverse events resulting in discontinuation were 13% in CP-CML, 11% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse events that led to treatment discontinuation were thrombocytopenia (4%) and infections (1%).
Dose modifications (dose delays or dose ~~reductions~~ reductions) due to adverse reactions occurred in 74% of the patients. The most common adverse reactions (≥5%) that led to dose modifications include thrombocytopenia (30%), neutropenia (13%), lipase increased (12%), rash (11%), abdominal pain (11%), pancreatitis (6%), and ALT, AST, or GGT increased (6%).

Table 4 5: Adverse Reactions Occurring in >10% of Patients, Any Group

	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
System Organ Class	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**
Cardiac or Vascular disorders								
Hypertension (a)	68	39	71	36	65	26	53	31
Arterial ischemia (b))*	~~13~~20	~~7~~11	~~12~~19	~~6~~9	~~8~~10	5	3	0
Cardiac Failure (c))*	~~6~~7	4	6	~~2 4~~	15	~~11~~8	6	~~6~~3
Nervous system disorders								
Peripheral neuropathy (g))*	~~1316~~	2	811	~~01~~	8	~~0~~	6	~~0~~

Footnotes from Table 5

Adverse drug reactions, reported using MedDRA and graded using NCI-CTC-AE v 4.0 (NCI Common Terminology Criteria for Adverse Events) for assessment of toxicity.
Treatment-emergent, all causality events
(a) derived from blood pressure (BP) measurement recorded monthly while on trial
(b) includes ~~cardiac, central nervous system~~cardiovascular, cerebrovascular, and peripheral ~~arterial~~ vascular ischemia
(c) includes cardiac failure, cardiac failure congestive, cardiogenic shock, cardiopulmonary failure, ejection fraction decreased, pulmonary edema, right ventricular failure
(d) includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort
(e) includes aphthous stomatitis, lip blister, mouth ulceration, oral mucosal eruption, oral pain, oropharyngeal pain, pharyngeal ulceration, stomatitis, tongue ulceration
(f) includes gastric hemorrhage, gastric ulcer hemorrhage, hemorrhagic gastritis, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, intra-abdominal hemorrhage, melena, rectal hemorrhage, and upper gastrointestinal hemorrhage
(g) includes burning sensation, skin burning sensation, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy
* represents an additional 13 months of follow-up

Table ~~5~~ 6: Serious Adverse Reactions (SAR)

	N (%)
Cardiovascular disorders	
Arterial ischemic event*	~~34~~53 (11.8%)
~~Myocardial infarction or worsening coronary artery disease~~	~~21(5%)~~
~~Stroke or TIA~~	~~8~~28 (6.2%)
Cardiovascular	~~7(2~~18 (4.0%)
Cerebrovascular	16 (3.6%)
Peripheral ~~arterial disease~~ vascular	
Hemorrhage	22 (4.9%)
CNS hemorrhage	10 (2.2%)
Gastrointestinal hemorrhage	10 (2.2%)
Cardiac failure*	~~20~~22 (4.9%)
Effusions[(b)(4)] a)	13 (~~3~~2.9%)
Atrial fibrillation	11 (2.4%)
Venous thromboembolism	10 (2.2%)
Hypertension	8 (~~2~~1.8%)
Gastrointestinal disorders	
Pancreatitis	23 (5.1%)
Abdominal pain	17 (~~4~~3.8%)
Blood and lymphatic system disorders	
Febrile neutropenia	13 (~~3~~2.9%)
Thrombocytopenia	13 (~~3~~2.9%)
Anemia	12 (2.7%)

Infections	
Pneumonia	24 (45.3%)
Sepsis	11 (2.4%)
General	
Pyrexia	14 (3.1%)

(a)includes pericardial effusion, pleural effusion, and ascites
* represents an additional 13 months of follow-up

Laboratory Abnormalities
Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML (see Table 67).

Table 6 7: Incidence of Clinically Relevant Grade 3/4* Hematologic Abnormalities

Table 78: Incidence of Clinically Relevant Non-Hematologic Laboratory Abnormalities

Laboratory Test	**Safety Population N=449**	
	Any Grade* (%)	**G3CTCAE Grade 3/4 (%)**

6. Under Section 7, Drug Interactions, in the FPI, the team removed the following statement regarding a starting dose of 30 mg in patients taking CYP3A inhibitors.

7.1 Drugs That Are Strong Inhibitors of CYP3A Enzymes
In a drug interaction study in healthy volunteers, co-administration of Iclusig with ketoconazole increased plasma ponatinib $AUC_{0\text{-}inf}$ and C_{max} by 78% and 47%, respectively *[see Clinical Pharmacology (12.3)]*. When administering Iclusig with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole), the recommended starting dose should be reduced ~~to 30 mg once daily~~*[see Dosage and Administration (2.1)]*. Patients taking concomitant strong inhibitors may at increased risk for adverse reactions *[see Clinical Pharmacology (12.3)]*.

7. Under Section 8, Use in Specific Populations, additional information was added to include data in patients older than 65 who experienced a vascular event.

8.5 Geriatric Use

One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (38%) as compared with patients < 65 years of age (64%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a higher major hematologic response rate (47%) as compared with patients < 65 years of age (40%). Forty-six percent of patients ≥ 65 years had vascular occlusion events. Patients of age ≥ 65-years ~~may be~~ are more likely to experience adverse reactions including vascular occlusion decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

8. Under Section 12, Clinical Pharmacology, a new sub-section entitled Pharmacodynamics (12.2) was added to the FPI to reflect current dose exposure data. In addition, a minor editorial revision was made to section 12.3 Pharmacokinetics.

12.2 Pharmacodynamics

In a cell-based assay, ponatinib concentrations of 20 nM (10.65 ng/mL) were sufficient to suppress most BCR-ABL mutant clones. However, ponatinib concentrations of 40 nM (21.3 ng/mL) were required to suppress T315I mutants. The median and range of steady-state C_{max} and trough (C_{min}) concentrations of ponatinib following 29 days of once-daily dosing of 15 mg, 30 mg and 45 mg are listed in Table 9.

Table 9: Median, Maximum, and Minimum Ponatinib Exposure at Steady-State by Dose Group: PK Evaluable Population

Dose	Median C_{max} (Range) (nM)	Median C_{min} (Range) (nM)
15 mg QD (n = 8)	49 (23 – 105)	28 (11 – 68)
30 mg QD (n = 9)	125 (67 – 178)	54 (41 – 89)
45 mg QD (n = 21)	161 (64 – 336)	67 (22 – 137)

Concentrations of ponatinib shown in cell-based assays to suppress unmutated BCR-ABL and most mutant BCR-ABL clones may be achieved at once daily dosing of 15 mg or 30 mg.

The dose intensity-safety relationship indicated that there are significant increases in grade ≥ 3 adverse events (hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) over the dose range of 15 to 45 mg once-daily.

12.3 Pharmacokinetics

Drug Interactions

Coadministration of Ponatinib and CYP3A Inhibitors

Coadministration of a single 15 mg oral dose of ponatinib in the presence of ketoconazole (400 mg daily), a strong CYP3A inhibitor, to 22 healthy volunteers, ~~increases~~ increased the $AUC_{0-\infty}$ and C_{max} of ponatinib by 78% and 47%, respectively, when compared to administration of ponatinib alone *[see Drug Interactions (7.1)]*.

9. Section 14, Clinical Studies, of the FPI was updated to include the new information from FDA's analysis of the safety data. The table numbers in this section have also been re-numbered.

14 CLINICAL STUDIES

The safety and efficacy of Iclusig in patients with CML and Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy were evaluated in a single-arm, open-label, international, multicenter trial. Efficacy results described below should be interpreted within the context of updated safety information *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precaution (5.1, 5.2)]*

All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; or blast phase CML /Philadelphia-positive acute lymphoblastic leukemia [BP-CML]/Ph+ ALL), resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation.

At the time of analysis, the median follow-up was 10 months (minimum of 6 months of follow-up for all ongoing patients). Baseline demographic characteristics are described in Table ~~8~~ 10.

Table ~~8~~ 10: Demographic and Disease Characteristics

Disease History	
Median time from diagnosis to first dose, years (range)	6.1 (0.3 to 28.5)
Resistant to Prior TKI Therapy, n (%)	374 (88%)
Presence of one or more BCR-ABL kinase domain mutations*	244 (55%)

*Of the patients with one or more BCR-ABL kinase domain mutations detected at entry, 37 unique mutations were detected.

10. Section 17, Patient Counseling Information has been updated to reflect the new safety concerns associated with taking Iclusig. Risks of vascular occlusion, heart failure, cardiac arrhythmias, neuropathy, and ocular toxicity.
References within have been updated to align with the revised order under Section 5, Warnings and Precautions.

17 PATIENT COUNSELING INFORMATION

~~**Thrombosis and Thromboembolism**~~

Vascular Occlusions

Inform patients that serious arterial thromboses (including arterial stenosis sometimes requiring revascularization) and venous thromboembolism events have occurred. Advise patients to immediately contact their health care provider with any symptoms suggestive of a blood clot such as chest pain, shortness of breath, weakness on one side of the body, speech problems, leg pain, or leg swelling *[see Warnings and Precautions (5.1)]*.

Heart Failure and Cardiac Arrhythmias
Inform patients of the possibility of heart failure, and abnormally slow or fast heart rates. Advise patients to contact their health care provide if they experience symptoms such as shortness of breath, chest pain, palpitations, dizziness, or fainting *[see Warnings and Precautions (5.2, 5.10)]*.

Hepatotoxicity
Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately contact their health care provider if signs of liver failure occur, including yellowing of the eyes or skin, "tea"-colored urine, or drowsiness *[see Warnings and Precautions (5~~2~~.3)]*.

~~Congestive Heart Failure and Cardiac Arrhythmias~~
~~Inform patients of the possibility of congestive heart failure, and abnormally slow or fast heart rates. Advise patients to contact their health care provide if they experience symptoms such as shortness of breath, chest pain, palpitations, dizziness, or fainting *[see Warnings and Precautions (5.3, 5.8)].*~~

Neuropathy
Inform patients of the possibility of developing peripheral or cranial neuropathy while being treated with Iclusig. Advise patients to report symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness *[see Warnings and Precautions (5.6)]*.

Ocular Toxicity
Inform patients of the possibility of ocular toxicity while being treated with Iclusig. Advise patients to report symptoms of ocular toxicity, such as blurred vision, dry eye, or eye pain *[see Warnings and Precautions (5.7)]*.

Hemorrhage
Inform patients of the possibility of serious bleeding and to immediately contact their

health care provider with any signs or symptoms suggestive of hemorrhage such as unusual bleeding or easy bruising *[see Warnings and Precautions (5 ~~6~~.8)]*.

Fluid Retention
Inform patients of the possibility of developing fluid retention and to contact their health care provider for symptoms such as leg swelling, abdominal swelling, weight gain, or shortness of breath *[see Warnings and Precautions (5.~~7~~9)]*.

Myelosuppression
Inform patients of the possibility of developing low blood cell counts; inform patients to report immediately should fever develop, particularly in association with any suggestion of infection *[see Warnings and Precautions (5.~~9~~11)]*.

Compromised Wound Healing and Gastrointestinal Perforation
Advise patients to inform their health care provider if they plan to undergo a surgical procedure or had recent surgery *[see Warnings and Precautions (5.~~11~~13)]*.
Inform patients that cases of gastrointestinal perforation have been reported *[see Warnings and Precautions (5.~~12~~13)]*.

Embryo-Fetal Toxicity
Inform patients that Iclusig can cause fetal harm when administered to a pregnant woman. Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions (5.~~12~~14) and Use in Specific Populations (8.1)]*.

Recommendations

With the identification and subsequent analysis of new safety information, the FDA team acted under the provisions of FDAAA to require Ariad to make safety labeling changes, create a REMS that provides for a communication plan that describes the new safety risks, and additional post marketing studies. Ariad has agreed to the revisions outlined in this review, and the team recommends approval of S-007 and S-008. Final clean (agreed-upon PI) is attached.

Diane Hanner/ Theresa Carioti	December 20, 2013
Regulatory Project Manager	Date
Lara Akinsanya	December 23, 2013
Acting Chief, Project Management Staff	Date

Following this page, 19 pages withheld in full - Duplicate copy of package insert 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.

/s/

THERESA A CARIOTI
12/23/2013

MONSURAT O AKINSANYA
12/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	December 10, 2013
Reviewer(s):	Naomi Redd, PharmD, Risk Management Analyst DRISK
	Joyce Weaver, PharmD, Senior Risk Management Analyst DRISK
	Kate Heinrich Oswell, Senior Health Communications Analyst, DRISK
Team Leader:	Cynthia LaCivita, PharmD, Team Leader DRISK
Division Director:	Claudia Manzo, PharmD, Division Director DRISK
Drug Name(s):	ponatinib (Iclusig®)
Therapeutic Class:	Tyrosine Kinase Inhibitor
Dosage and Route:	15mg and 45mg tablet
Application Type/Number:	NDA 203469
Submission Number:	December 5, 2013 Supplement 8; DARRTS sequence 88
Applicant/sponsor:	ARIAD Pharmaceuticals, Inc.
OSE RCM #:	2013-2280
TSI #:	1347

CONTENTS

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the need for a risk evaluation and mitigation strategy (REMS) and Ariad's proposed REMS submitted on December 5, 2013 Supplement 8, sequence 88 for Iclusig (ponatinib). Iclusig is an orally-active tyrosine kinase inhibitor (TKI) that is active against the un-mutated and mutated BCR-ABL gene; indicated 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.[1]

Iclusig was approved December 2012 without a REMS. At the time of approval, the drug label contained information about the risks of arterial thrombosis and hepatotoxicity in the Boxed Warning, and Warnings and Precautions sections. Serious arterial thrombosis events which included cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke, occurred in 8% of Iclusig-treated patients, and venous thromboembolic events occurred in 3% of patients.[2] Post approval, the Agency became aware of new clinical trial and spontaneous post marketing reports indicating an increase of arterial and venous occlusions now reported in 27% of all patients. Vascular occlusion events reported include fatal and life threatening myocardial infarction and stroke, distal extremity necrosis and gangrene requiring amputation, urgent revascularization procedures (cerebrovascular, coronary, peripheral arterial), visual loss, blindness, and retinal vein occlusion.[3] New adverse event information, in addition to an increase in reported safety information, led to voluntary market suspension of Iclusig on October 31, 2013.

The agency considers the aforementioned risks to be "new safety information" as defined in section 505-1(b) (3) of the FDCA. The Agency has required Araid to revise labeling and require a REMS to ensure the benefits of Iclusig outweigh the risks of the increased frequency and magnitude of thromboembolic adverse events.

The review team (DHP and DRISK) and senior CDER management deliberated on the elements of the REMS that would be necessary to ensure that the benefits of Iclusig outweighed the risks. A communication plan REMS was considered as was a REMS that required elements to assure safe use in addition to a communication plan. Taking into account the patient population likely to use the drug, the characteristics of the healthcare providers likely to prescribe the drug, and the perceived impact of three Drug Safety Communications and voluntary suspension of sales and marketing, senior CDER management determined that a communication plan that provided targeted and specific communications to healthcare providers about the risks and updated appropriate use of the Iclusig should be required. DHP also supported a REMS with these elements. Although DRISK supported a REMS with elements to assure safe use that included

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[1] Iclusig Prescribing Information December 2012

[2] FDA Drug Safety Communication October 11, 2013

[3] REM Memorandum entered in DARRTS November 25th, 2013

pharmacy certification and a safe use condition that included a prescription authorization form with key safety messages, DRISK will align with the recommendations of the group.

1 INTRODUCTION

This review by the DRISK evaluates the need for a REMS for Iclusig (ponatinib) based on new post marketing safety information and Ariad's proposed REMS submitted on December 5, 2013, Supplement 8, sequence 88.

Iclusig is currently indicated 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.[1] Iclusig was approved December 2012 without a REMS.

Post approval the Agency became aware of new clinical trial and spontaneous post marketing reports indicating an increase of arterial and venous occlusions in patients receiving Iclusig. There are also reports of increased magnitude of occlusive events overall, new vascular occlusive events involving the eye (loss of vision due to blood clots), and occlusion of mesenteric blood vessels. Documented cases of adverse events show an overall increase in frequency of vascular occlusions, manifested as stroke, myocardial infarction, peripheral vascular disease with ischemic necrosis, and other vascular occlusive events.[2] The agency considers this to be "new safety information" as defined in section 505-1(b) (3) of the FDCA.

Drug Safety Communications (DSC) were issued on October 11 and 31, 2013 to convey these risks. Ariad voluntarily suspended marketing of Iclusig on October 31, 2013 and a third DSC was issued on November 5, 2013 to inform patients and providers on how to access Iclusig post market suspension.

1.1 BACKGROUND

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of one-two cases per 100,000 adults and accounts for approximately 15% of newly diagnosed cases of leukemia in adults[4]. Genetic translocations in the Philadelphia chromosome results in the formation of an oncoprotein BCR-ABL that leads to an oncogenic expression that elevates tyrosine phosphokinase activity.[5] Significant mutations can occur in the kinase domain of BCR-ABL, specifically the T315I mutation, which can impair the activity of tyrosine kinase inhibitors (TKIs).[4] The T315I mutation displays resistance to many of the currently available TKIs, and patients who develop this mutation have a poorer prognosis.[6]

Iclusig is a potent orally-active tyrosine kinase inhibitor (TKI) that is active against un-mutated and mutated BCR-ABL, including the threonine to isoleucine mutation at

[4] Jabbour E, et al. Chronic myeloid leukemia: 2012 update on diagnosis, monitoring, and management.2012 Wiley Periodicals

[5] Kurzrock R, et al. Philadelphia chromosome-positive leukemias: from basic mechanisms to molecular therapeutics. Ann Intern Med. May 20, 2003; 138(10):819-30

position 315 (T315I), which is present in up to 20% of patients with tyrosine kinase inhibitor-resistant disease, and confers resistance to all other approved BCR-ABL tyrosine kinase inhibitors.[6] Ponatinib has demonstrated significant anti-leukemic activity in patients with CML and those with Ph-positive ALL, including in patients with the T315I mutation.[7]

1.2 REGULATORY HISTORY

- November 20, 2009: Iclusig was granted Orphan Designation for the treatment of CML and for the treatment of Philadelphia chromosome-positive Ph+ALL
- November 30, 2010: Iclusig was granted Fast Track designation for the same proposed indications
- December 2012: Iclusig received accelerated approval under subpart H
- October 11, 2013: initial Drug Safety Communication (DSC)
- October 18, 2013: termination of Phase 3 trial
- October 31, 2013: second DSC, and ARIAD suspends marketing and sales
- (b) (4)
- November 25, 2013: Letter to Ariad, New safety information requiring labeling supplement, REMS and PMR
- November 25, 2013: REMS Memorandum to File
- December 5, 2013: Ariad's proposed REMS Supplement 8; DARRTS sequence number 88
- Iclusig draft label, submitted via email on December 5, 2013

2 MATERIALS REVIEWED

- DRISK Risk Management Review, signed in DARRTs November 28, 2012 Cynthia LaCivita, Pharm.D.
- Cross-Discipline Team Leader Review and addendum signed in DARRTS, December 3 and 5, 2012
- Clinical Review of Efficacy and Safety in DARRTS November 19, 2012, by R. Angelo de Claro, M.D.
- Iclusig Prescribing Information December 2012
- FDA Drug Safety Communication: FDA investigating leukemia drug Iclusig (ponatinib) after increased reports of serious blood clots in arteries and veins October 11, 2013; October 31, 2013, and November 5, 2013
- Memorandum of teleconference meeting minutes with FDA and ARIAD. Subject: Procedure for disseminating Single Patient INDs/Emergency INDs,

[6] Cortes J.E., et al. A Phase 2 Trial of Ponatinib in Philadelphia Chromosome-Positive Leukemias. NEJM; November 7, 2013; 369 (19): 1783-1796.

[7] Clinical Review of Efficacy and Safety by R. Angelo de Claro, MD entered in DARRTS November 19, 2012

status of REMS and Expanded Access Protocol submissions. November 4, 2013

- REMS Memorandum found in DARRTs November 25, 2013
- FDAAA Letter November 25, 2013
- ARIAD's proposed REMS and REMS Supporting Document, submitted on December 5, 2013 eCTD sequence number 0081and 0083

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

Serious vascular occlusion events were reported in 8% of patients during the review of the original new drug application (NDA). Additional clinical trial data and spontaneous post marketing reports have provided new safety information indicating an increase of arterial and venous occlusions that are now reported in 27% of all patients.[2] Vascular occlusion events reported include fatal and life threatening myocardial infarction and stroke, distal extremity necrosis and gangrene requiring amputation, urgent revascularization procedures (cerebrovascular, coronary, peripheral arterial), visual loss, blindness, and retinal vein occlusion.[3] These newly reported adverse events and increased frequency of previously known vascular occlusive adverse events led to voluntary market suspension of Iclusig on October 31, 2013.

Clinical trial follow-up shows a substantial change in the safety profile due to a continuing increase in vascular occlusive events, and present data indicate that at least 51% (25/49) of patients in the initial phase 1 trial have developed vascular occlusion events over a median treatment duration of 2.7 years. In the phase 2 single arm, single agent trial, over a median treatment duration of 1.3 years, at least 24% have developed vascular occlusions.[3] The events included fatal and life threatening myocardial infarction and stroke, severe narrowing of blood vessels in the extremities, and the need for urgent surgical procedures to restore blood flow.[2] There were also reported cases of distal extremity necrosis and gangrene requiring amputation. Newly identified serious adverse reactions have also been reported involving the eyes, including blindness, decreased vision, and clots in the blood vessels of the eye.[2] The table below is a summary of vascular occlusion rates in age groups with and without risk factors:[3]

Patient Age	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia	No history of ischemia, hypertension, diabetes, or hyperlipidemia
Age: 49 or younger	18% (6/33)	12% (13/112)
Age: 50 to 74 years	33% (50/152)	18% (20/114)
Age: 75 and older	56% (14/25)	46% (6/13)
All age groups	33% (70/210)	16% (39/239)
Total	24% (109/449)	

Based on these newly reported adverse events and increased frequency of previously known vascular occlusive adverse events, the Agency issued a DSC on October 11, 2013 to announce it was investigating the increased frequency of reports of serious and life-threatening blood clots and severe narrowing of blood vessels in patients treated with Iclusig. Recommendations at that time were made for healthcare professionals to consider whether the benefits of Iclusig treatment are likely to exceed the risk of treatment. Further information from ponatinib clinical trials revealed more vascular occlusive adverse events, which prompted the FDA to request the voluntary suspension of sales and marketing of Iclusig and to issue a second DSC on October 31, 2013, announcing the suspension of sales and marketing.

A third DSC was sent on November 5, 2013 to address access needs to patients who were currently receiving treatment with ponatinib. This DSC stated that new patients should not be started on Iclusig unless no other treatment options are available and all other therapies have failed. Existing patients would be eligible to receive ponatinib under an Investigational New Drug (IND) application. IND applications were sent to the Agency for patients to either continue or start therapy (as deemed necessary by the prescribing physician). Meeting minutes from a teleconference with Ariad on November 4th, 2013 indicated that since approval in December 2012, (b) (4) patients have received ponatinib; there are (b) (4) patients actively receiving ponatinib therapy, and there have been (b) (4) prescribers since Iclusig was approved.

3.2 Applicant's Proposed Risk Evaluation and Mitigation Strategy

3.2.1 Background

(b) (4)

On November 25, 2013, based on "new safety information" as defined in section 505-1(b)(3), the Agency issued a letter that notified Ariad that safety labeling changes and a post-approval REMS were necessary as well as the requirement to perform additional post marketing requirements for Iclusig. Ariad was instructed to develop a REMS and the necessary elements should include a communication plan to address the risk of serious of life-threatening blood clots and severe narrowing of blood vessels (arteries and veins) and timetable for submission of assessments. Ariad submitted a proposed REMS on December 5, 2013.

3.2.2 Goals

(b) (4)

Reviewer comment: The sponsor's proposed goal is not acceptable, as it should be revised to reflect the restricted indication and updated risk messaging. DRISK proposes the following changes for the goal:

(b) (4)

- [redacted]:
    - *Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).*
    - *Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.*
- *Informing prescribers of the serious risks of vascular occlusion and thromboembolism associated with ICLUSIG treatment.*

3.2.3 Communication Plan

The proposed REMS includes: a Dear Healthcare Provider (HCP)REMS Introductory Letter, a Dear Professional Society REMS Introductory Letter, REMS Fact Sheet, Journal Information Piece, commitment to make REMS information available at select scientific meetings, and an Iclusig REMS Website.

- *Dear Healthcare Provider Letter (DHCP) REMS Introductory Letter and Dear Professional Society (DPS) REMS Introductory Letter* – The DHCP REMS Introductory Letter will be sent electronically (via email) or by the US Postal Service to hematologists, oncologists and other healthcare providers known or likely to prescribe Iclusig. The letter will inform prescribers about the serious risk of vascular occlusion associated with Iclusig. The sponsor will also distribute the Introductory Letter to the professional societies: American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH), with a request to distribute the letter to their membership. Both letters will be distributed within [redacted] days after the REMS approval date, and will be available from the *Iclusig REMS Website* (www.IclusigREMS.com) at the time of the mailing and will remain on the website for [redacted].
- *REMS Fact Sheet* – An Iclusig REMS Fact Sheet will be available for HCPs as a quick Iclusig REMS reference tool. This fact sheet will be included in the DHCP letter and DPS mailings, and available on the Iclusig REMS website. Hard copies will also be distributed by Ariad's sales representatives and medical field-based personnel.
- *Journal Information Piece* – Ariad will publish an information piece about the risks of Iclusig in the Journal of Clinical Oncology and Blood. The information piece will be published [redacted] following Iclusig REMS approval. Ariad will also display updated risk information and REMS materials through professional scientific meetings, in particular ASCO and ASH, for [redacted] following REMS approval.
- Iclusig REMS Website – will be available within [redacted] days of the REMS approval, and will contain information on the Iclusig REMS such as the US PI and Iclusig REMS Fact Sheet. This information will remain on the webpage for [redacted].

Reviewer comment: In general the types of communication pieces are reasonable. However, significant changes are necessary to provide clear risk messaging and to ensure the dissemination frequency is sufficient to reach the target audience. The necessary comments are included as track changes in the aforementioned materials.

3.2.4 Timetable for Submission of Assessments

ARIAD proposed submitting REMS Assessments to FDA 1 year, 3 years and 7 years from the date of initial approval of the REMS.

Reviewer comment: The proposed timetable for submission of assessments is acceptable.

3.2.5 Information Needed for Assessment

The REMS Supporting Document stated that ARIAD would conduct periodic assessments of the extent to which the REMS elements are meeting the goals and objectives. (b) (4) is the source proposed to be used to assess if the REMS is meetings the educational goal. In addition they propose to (b) (4).

Reviewer comment: In general the proposed assessment plan appears reasonable; however, additional comments are likely after we consult with the REMS assessment team and DHP.

3.3 RISK MANAGEMENT OPTIONS

Revisions to labeling and requiring a REMS were determined to be necessary strategies to improve the risk benefit profile for Iclusig. Several REMS options were considered to inform prescribers of the revised indications, the newly observed adverse events and the increased frequency of previously known thromboembolic adverse events, as outlined below.

3.3.1 Product Labeling

The December 2012 US Prescribing Indication for Iclusig is 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.

DHP is currently engaged in labeling negotiations with Ariad to revise and narrow the indications for Iclusig. The proposed revised indications are:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

At the time of approval, the drug label contained information about the risks of arterial thrombosis and hepatotoxicity in the Boxed Warning, and Warnings and Precautions sections. Serious arterial thrombosis events which included cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke, occurred in 8% of Iclusig-treated patients, and venous thromboembolic events occurred in 3% of patients.[2]

Updates to labeling also included revisions to the Boxed Warning and section 5.1 of the Warnings and Precautions to include updated risk information on vascular occlusion. The Medication Guide was also updated in this supplement.

Reviewer Comments: DHP has revised the label to better identify and restrict the indicated patient population and is important to inform providers about safe and appropriate use of the drug. Changes to the indicated populations will assist in identification of patients with leukemia progression and are at greatest risk versus those who may still have alternative options and may thus avoid or postpone exposure to this vascular risk.

3.3.2 REMS Options

Option 1: REMS with a Communication Plan

The rationale for this option was to inform prescribers of new safety information in the revised PI. DHP favored this option as it would be less burdensome on prescribers, and the communication plan could be of limited duration. DRISK was concerned with this option because previous experience with other REMS communication plans has demonstrated that REMS comprising voluntary education or a communication plan usually results in low stakeholder awareness of the REMS materials and risk messages.

Option 2: REMS with Communication Activities, Pharmacy Certification, and Prescription Authorization form as documentation of safe use

The rationale for this option would be to convey pertinent information to all prescribers on the revised indication and new safety information for Iclusig. DRISK preferred this option as it would provide a required pathway for prescribers to receive the relevant information. An advantage of this option is that the prescription authorization form would include the pertinent risk messages and updated labeling information; therefore prescribers would receive this information at the time of prescribing. Furthermore, this option would not require certification of prescribers prior to dispensing. During the discussion of REMS options, a concern was stated that requiring a prescription authorization form for each prescription may be burdensome for the prescriber. To address this concern, the prescription form could be valid for more than a 30-day time frame, decreasing the number of times the prescriber would need to access the prescription authorization form.

Option 3: REMS with Communication Activities, Provider and Pharmacy Certification, and Prescription Authorization form as documentation of safe use

DRISK and DHP also considered restricting distribution of Iclusig (ponatinib) under a REMS, such as would be accomplished through one time provider certification,

pharmacy certification, or other dispensing restrictions. DHP expressed concerns about the burden to providers and the potential to delay access to treatment.

3.4.3 Post Market Requirements

Post marketing requirements were determined to be necessary to better characterize risk factors for vascular events, to determine the incidence of these events when Iclusig is given with anticoagulant or antiplatelet therapy, and to characterize a safe dose range for Iclusig.

The Agency has required the sponsor to commit to 4 Post Marketing Requirements (PMRs) which are summarized below:

PMR 1: Propose and conduct an enhanced pharmacovigilance study of data from clinical trials and all post marketing sources to assess risk factors for, management of, and consequences of all vascular occlusive events that are serious or require medical evaluation or treatment, occurring while patients are receiving ponatinib or within 30 days of the last drug dose.

PMR 2: Conduct a prospective observational study to evaluate the incidence of and risk factors for vascular occlusive events when ponatinib is given with or without anticoagulant or antiplatelet agents. Submit a protocol that includes measures to ensure sufficient long term follow up to adequately capture late occurring vascular occlusive events and describe measures that minimize loss to follow-up.

PMR 3: Provide long-term follow-up of all patients enrolled in the Phase 1 (AP24534-07-101) and Phase 2 (AP24534-10-201) clinical trials (b) (4) assess the long-term safety of ponatinib treatment, including the long-term risk of vascular occlusive events. Include narratives for all cases of vascular occlusion (b) (4) (b) (4) For the Phase 3 trial, use a data cut-off date of 30 days following the last dose.

PMR 4: Conduct a randomized, multi-arm trial to characterize the safety of a range of ponatinib doses. The trial should be of sufficient size and duration to inform safe use of Iclusig in chronic phase CML. The trial should also assess the efficacy of the doses investigated. Include a plan for adequate PK sampling to provide exposure-toxicity and exposure-response data sufficient to identify appropriate dose ranges (or exposure targets) for patients with T315I mutation and for patients who have progressed after at least two TKIs and are considered to have no alternative therapy available.

4 DISCUSSION

Iclusig is a tyrosine kinase inhibitor that has demonstrated very high potency and broad specificity, including mutated forms of the protein that confer resistance to treatment with existing TKIs, including the T315I mutation for which no effective therapy exists.[8] The efficacy of Iclusig has been established in the use of patients with the T315I mutation, and despite the increase in adverse events that have occurred since product approval, at this time it appears this patient population and patients for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated would derive the most benefit from Iclusig. Although the actual incidence of vascular occlusive events with Iclusig is greater than what was reported in the original new drug application, Iclusig fills a need for therapy for patients with refractory CML and Ph+ ALL.

Currently there are 4 other TKIs FDA approved for the treatment of CML: imatinib (2001), dasatinib (2006), nilotinib (2007), and bosutinib (2012); all are oral therapies. Imatinib and dasatinib are also FDA approved for the treatment of Ph+ALL. Synribo (omacetaxine mepesuccinate) was approved October 2012 for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI). Synribo is administered subcutaneously and should be prepared in a healthcare facility and administered by a healthcare professional.

Iclusig (ponatinib) is currently the only TKI that provides activity to CML and Ph+ALL, in addition to resistance to the T315I mutation, making it an effective form of therapy when other TKIs are no longer active. Iclusig has been found to inhibit several other kinase regions, including VEGFR, whose inhibition has been found to result in arterial ischemic events. Iclusig is also relatively insoluble, which may cause precipitation and further contribute to the ischemic events found from VEGFR inhibition.[9] These pharmacodynamic factors make adverse events very likely to continue to occur in patients receiving Iclusig therapy.

Poorer outcomes and reduced overall survival rates are seen in patients that develop the T315I mutation. This mutation is present in up to 20% of patients with tyrosine kinase inhibitor-resistant disease, and confers resistance to all other approved BCR-ABL tyrosine kinase inhibitors[6], making the need for therapy in this patient population warranted. Revised product labeling to restrict the indication to a narrower population that includes treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL); and treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated, will help to mitigate the risks of vascular and occlusive events that may occur with Iclusig therapy.

[8] REMS Supporting Document, entered in DARRTS December 5, 2013

[9] CDTL Review by Virginia Kwitkowski entered in DARRTS December 3, 2012

The REMS options 1 and 2 (as stated above) were the two REMS largely considered by the review team; option 1 was preferred by DHP and option 2 was preferred by DRISK. These options were presented to and discussed with senior CDER management. In its deliberations, the review team and senior-level management within CDER considered that Iclusig is generally used by specialized prescribers (hematologists and oncologists). DRISK noted that experience from other REMS that reply only on voluntary communication activities often fail in delivering the risk messages to prescribers. DHP believes that the regulatory actions taken to date, including the voluntary suspension of sales and marketing, and the issuances of DSCs, have likely alerted the prescribing community about serious risks with Iclusig. Therefore, prescribers maybe more attuned to the safety issues and receptive to the risk messages contained in subsequent communications.

5 CONCLUSION

Taking into account the patient population likely to use the drug, the characteristics of the healthcare providers likely to prescribe the drug, and the perceived impact of the DSCs and voluntary suspension of sales and marketing, senior CDER management determined that a REMS that included a communication plan that provided targeted and specific communications to healthcare providers about the new safety information and updated appropriate use of the Iclusig should be required. DHP also supported a communication plan REMS. Although DRISK supported a REMS with elements to assure safe use, DRISK will align with the recommendations of the group for a communication plan REMS.

6 DRISK'S COMMENTS TO THE SPONSOR

1. General Comments:

FDA believes that much of the important risk messages of this REMS program, concerning new labeling and safety information have not been included in your proposed materials. We have provided templates for your materials including content and formatting. However, Ariad should incorporate any logos or other creative design to enhance ease of reader usability so that the materials are in a user-friendly format. Submit all program materials showing the actual layout and design.

The REMS, REMS attachments, and REMS Supporting Document must align with the final version of the full Prescribing Information and the REMS is still undergoing clearance in the Agency. Therefore, additional revisions will be necessary. Your submission should include a complete REMS document with the revised attachments showing the necessary changes. Please address all comments noted on the redlined documents in your submission. Accept all changes and submit both a Word tracked changes version and a Word clean version of each document, as well as a cover letter explaining all changes proposed in the documents.

The Agency will provide comments on the REMS assessments plan is still under review, comments will be forthcoming.

2. REMS document:

Please see the attached REMS document with the necessary changes with edits in track changes.

3. REMS Supporting Document:

We have not completed a full review of this document. At this time specify which third party databases will be used to obtain information on prescribers in order to send the REMS Dear Healthcare Provider Letter. Additional edits may be necessary.

4. REMS Letter to Healthcare Providers (email and print):

See FDA edited print version and electronic version template of REMS letters attached.

The subject of the emails should be "New Labeling and Safety Updates for Iclusig (ponatinib)." The outside of the mailed envelopes should state: "FDA Required REMS Safety Information." It should be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:

FDA Required REMS
Safety Information

5. REMS Letter for Professional Societies (email):

See electronic REMS Letter template attached.

6. REMS Factsheet:

See Factsheet template attached.

7. Journal Information Piece:

See Journal Information Piece template attached.

8. REMS Website:

Include a prominent link on the product website's homepage for REMS materials. This link should direct users to a separate REMS webpage that describes the REMS program risks of the REMS and lists only approved REMS materials.

Ensure the REMS website, is independent of the link to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the www.Iclusig.com website. The REMS website should also be accessible directly through a search engine.

Sponsor should submit screen shots and actual layout for the Iclusig REMS website.

We remind you to use bullets, moderate white space, shorter line lengths, and fewer lines of text when possible when developing your website. The following is a link to helpful guidelines developed by HHS that you may consider in developing your website.

http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes

See edited website overview and the REMS website template attached.

ATTACHMENTS

Following this page, 11 pages withheld in full - (b)(4) draft 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.

/s/

NAOMI B REDD
12/10/2013

CLAUDIA B MANZO
12/10/2013
concur

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS REVIEW

Date:	December 18, 2013
Reviewer(s):	Naomi Redd, PharmD, Risk Management Analyst, DRISK Joyce Weaver, PharmD, Senior Risk Management Analyst, DRISK Kate Heinrich Oswell, MA, Senior Health Communications Analyst, DRISK
Team Leader:	Cynthia LaCivita, Pharm.D, Team Leader, DRISK
Division Director:	Claudia Manzo, Pharm.D, Director, DRISK
Subject:	Proposed REMS with a communication plan
Drug Name(s):	Iclusig® (ponatinib)
Therapeutic class:	Tyrosine Kinase Inhibitor
Dosage forms:	15 mg and 45 mg
OND Review Division:	Division of Hematology Products (DHP)
Application Type/Number:	NDA 203469
Supplement # and Date	Supplement 8, sequence number 0091, December 18, 2013
Received:	December 18, 2013
Applicant/sponsor:	ARIAD
OSE RCM #:	2013-2280
TSI #:	1347

***** This document contains proprietary and confidential information that should not be released to the public. *****

1 INTRODUCTION

This review provides DRISK evaluation of the sponsor's proposed risk evaluation and mitigation strategy (REMS) for Iclusig® (ponatinib, NDA 203469) received December 5, 2013 as Supplement 8, sequence 88, and amended on December 18, 2013, sequence 0091. In this review, DRISK comments specifically on the REMS revisions submitted by the sponsor December 18, 2013.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSIONS

- Proposed REMS submitted December 6, 2013.
- Proposed REMS amendment submitted December 18, 2013.

2.2 DRISK REVIEWS FOR THE PROPOSED REMS SUBMISSION

- DRISK REMS review dated December 10, 2013.

3 REVIEW FINDINGS

- The sponsor concurred with DRISK's necessary changes and editorial revisions to the proposed REMS for Iclusig. Below is a summary of necessary changes that are in addition to the comments that were included in the December 10, 2013 DRISK REMS review. A summary of these revisions are below and can also be found in DARRTS on the corresponding dates.

Summary of REMS Modifications and Revisions	
December 12, 2013	REMS Document • Revisions of the goals to include "inform" versus "(b) (4) the risks. • Revision of the time frame of when the REMS elements will be enacted from (b) (4) days to 15 days from the REMS approval date. • Request to send the print versions of the REMS health care provider (HCP) and Professional Society Letters. REMS Fact Sheet, Journal Piece, and Website – Addressed the need to increase the font size, decrease the white space, and change the color of the headings to improve readability. REMS Supporting Document - Comment to removed promotional language
December 13, 2013	REMS Document – Change "(b) (4)" to "21 days" REMS Assessment Plan - Request to use a tracking system for opened or unopened emails sent to HCPs. REMS Letter- Included language in the print version of the HCP and Professional Society Letters that the safety information is "enclosed."
December 16, 2013	REMS Document- Changes in the language of the goals from "(b) (4)

	population to the "limited" population. And instructions to make the corresponding changes in the REMS materials. REMS Supporting Document - Removal of (b) (4) from the REMS supporting document as this is not needed for a communication plan REMS.

DRISK finds the sponsor's new proposed revisions to the REMS materials submitted on December 18, 2013 acceptable.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK finds Ariad's proposed amended Iclusig REMS and appended materials, and REMS Supporting Document submitted on December 18, 2013 acceptable and recommends approval of the REMS. A clean copy of the REMS is appended.

Following this page, 15 pages withheld in full - Duplicate copy of REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAOMI B REDD
12/18/2013

CLAUDIA B MANZO
12/18/2013
concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203469/S-007 & S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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ARIAD®

27 November 2013

SAFETY LABELING CHANGES UNDER 505(o)(4)
PRIOR APPROVAL SUPPLEMENT

Robert C. Kane, MD.
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0085

Attn: Ms. Diane Leaman, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This prior approval supplement concerns the New Drug Application (NDA) 203469 for Iclusig® (ponatinib) 15 mg and 45 mg tablets for oral use, submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD). Iclusig was granted accelerated approval on 14 December 2012 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 (TKI) therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior TKI therapy. ARIAD has temporarily suspended marketing of Iclusig while revisions to the US prescribing information (USPI) and medication guide and the implementation of a risk evaluation and mitigation strategy (REMS) are under review by FDA.

Your safety labeling change notification letter dated 25 November 2012 stated that FDA have identified "new safety information" as defined in section 505-1(b)(3) of the Food Drug and Cosmetic Act; specifically an increase in frequency of vascular occlusions in patients receiving Iclusig. In the safety labeling change notification letter ARIAD was requested to address this new safety information in the INDICATIONS AND USAGE, BOXED WARNING, DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS sections of the US prescribing information (USPI) and medication guide.

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In this prior approval supplement, ARIAD has updated the draft USPI and medication guide addressing the changes requested by FDA in the safety labeling change notification. A few additional modifications have been made to the USPI which are described below and identified in the tracked changes version of the USPI. The only sections of the USPI where ARIAD has proposed meaningful changes are the indications and usage and dosage and administration sections. Changes in those sections are described in the sections below. However, we believe that the changes in both sections are in keeping with the requests expressed in the safety labeling change notification letter. Also addressed below are two additional changes the Agency may wish to consider in section 5.1 of the warnings and precautions (vascular occlusion), and ARIAD's response to two requests made in comments embedded in the version of the USPI received from FDA in the safety labeling change notification letter.

Indications and Usage:
ARIAD has revised the indication statement to the one proposed (b) (4) As discussed (b) (4), ARIAD believes that this proposed indication statement would permit the use of Iclusig only when all other reasonable options have been exhausted, is encompassed by the population studied in the PACE trial, and allows physicians to use Iclusig in a way that is consistent with current medical practice and the use of TKI therapy. ARIAD believes that these are populations where the benefit-risk remains clearly favorable and is in keeping with the request in the safety labeling change notification letter "to provide additional restriction to the indicated population of patients after prior kinase therapy, to those patients who have no other alternative treatment options that are available or appropriate". The indication statement proposed by ARIAD is below

Iclusig (ponatinib) is a kinase inhibitor indicated for the:

- *Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) and T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).*
- *Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor therapy is indicated.*

Dosage and Administration:
ARIAD has accepted the suggestion made by FDA in the USPI received in the drug safety communication letter (also received (b) (4)). However, as ARIAD's recommendation was based on both our analysis of the data on dose reduction of responding phase 2 patients, and our view that there is a relationship between dose and the risk of vascular occlusive events, we would welcome continued discussion of this type of specific dose reduction instructions when the Agency deems it appropriate. Nonetheless, in response to the statement in the drug FDA safety labeling communication letter "to inform prescribers of options to consider in achieving a more favorable benefit: risk relationship for use of Iclusig", ARIAD has proposed the following statement in section 2.1 of the USPI: "*Consider*

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reducing the dose of Iclusig for CP CML and AP CML patients who have achieved a major cytogenetic response."

Other considerations:
ARIAD has not proposed any major changes to the sections of the USPI addressing patient safety or the adverse reactions observed in the clinical development program. However, we do believe that the Agency should review those sections of the USPI and, in doing so, consider two revisions to section 5.1 of the warnings and precautions (vascular occlusion) described below.

- In the last sentence of the first paragraph, the following sentence was inserted: (b) (4) [redacted]" We acknowledge that in some subgroups the incidence of vascular occlusion exceeds the overall incidence in the broader population and that events of vascular occlusion have occurred at doses lower than 45 mg. However, data from small subgroups considered retrospectively introduce potential bias and may not represent the broader population. Ideally, these conclusions would be confirmed. Therefore, in consideration the small subgroup referenced in the text by FDA and ARIAD's plans to further prospectively evaluate the impact of dose on vascular occlusive events, ARIAD asks that the FDA reconsider the inclusion of this statement.
- In the last sentence of the second paragraph, the following sentence was inserted by FDA: (b) (4) [redacted]. ARIAD has further reviewed this individual case of a 73 year old male with a history of three prior myocardial infarctions, hypertension, hypercholesterolemia, diabetes, cirrhosis of the liver and pancreatitis (patient 023-001). The patient had dose reductions for a variety of complications (e.g., LFT abnormalities in the progression of pre-existing cirrhosis), and had his aspirin and clopidogrel discontinued while on the trial after which he suffered another myocardial infarction. In consideration of the confounding factors of this individual case and that the statement that appears before this sentence already expresses the concept that event can occur at dose intensities lower than 30 mg, ARIAD asks that the FDA reconsider the inclusion of this statement.

Response to FDA requests:
Finally, we would like to address the two requests provided as comments (b) (4) [redacted]. The first request was to submit (b) (4) [redacted] The second request was to (b) (4) [redacted].

SUBMISSION COMPONENTS:
The basis for the draft USPI was the version appended to the 25 November 2013 safety labeling change notification letter. In the track changes version we have accepted any changes we agreed

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to and edited over the ones that we do not agree with. This prior approval supplement includes the following components.

- Iclusig Draft USPI
  - Clean Word
  - Clean PDF
  - Track Changes Word
  - Track Changes PDF
- Iclusig Draft Medication Guide
  - Clean Word
  - Clean PDF
  - Track Changes Word
  - Track Changes PDF

SUBMISSION TECHNICAL SPECIFICATIONS:
ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008)*. This submission consists of Module 1 documents. The submission is approximately 2.0 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 26 November 2013.

If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

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27 November 2013

SUPPLEMENT 007
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

Robert C. Kane, MD.
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0086
Response to 25 November 2013 Request for Information

Attn: Ms. Diane Leaman, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This amendment concerns the prior approval supplement (PAS-007) proposing safety labeling changes under 505(o)(4) submitted on 27 November 2013 (NDA 203469, sequence 0085) to the New Drug Application (NDA) 203469 for Iclusig® (ponatinib), submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD). Iclusig was granted accelerated approval on 14 December 2012 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 (TKI) therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior TKI therapy. ARIAD has temporarily suspended marketing of Iclusig while revisions to the US prescribing information (USPI) and medication guide and the implementation of a risk evaluation and mitigation strategy (REMS) are under review by FDA.

Please refer to (b) (4)

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[redacted] (b) (4) At the request of FDA that (b) (4) [redacted]. In a teleconference held between representatives of ARIAD and the FDA on 26 November 2013, it was agreed that the information request would be responded to within PAS-007 because (b) (4) has, at the request of FDA, been withdrawn. A partial response to the 25 November 2013 request for information is included in this amendment with the other submission components described below:

- Response to FDA Information Request items 1a and 1b (1.11.3 Efficacy Information Amendment)
- ADER3.xpt and data definition table (define.pdf)
  - SAS program for ADER3.xpt
- MH.xpt and data definition table (define.pdf)
- ADSL_FDA.xpt and data definition table (define.pdf)

SUBMISSION TECHNICAL SPECIFICATIONS

ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008)*. This submission consists of Module 1 documents. The submission is approximately 7.5 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 26 November 2013.

If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg

Digitally signed by Andrew P Slugg
DN: cn=Andrew P Slugg, o=ARIAD Pharmaceuticals, Inc., ou=Regulatory Affairs, email=andrew.slugg@ariad.com, c=US
Date: 2013.11.27 14:13:30 -05'00'

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

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03 December 2013

SUPPLEMENT 007
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

Robert C. Kane, MD.
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0087
Response to 25 November 2013 Request for Information

Attn: Ms. Diane Leaman, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This amendment concerns the prior approval supplement (PAS-007) proposing safety labeling changes under 505(o)(4) submitted on 27 November 2013 (NDA 203469, sequence 0085) to the New Drug Application (NDA) 203469 for Iclusig® (ponatinib), submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD). Iclusig was granted accelerated approval on 14 December 2012 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 (TKI) therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior TKI therapy. ARIAD has temporarily suspended marketing of Iclusig while revisions to the US prescribing information (USPI) and medication guide and the implementation of a risk evaluation and mitigation strategy (REMS) are under review by FDA.

Please refer to (b) (4)

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(b) (4)

t the request of FDA that (b) (4)

In a teleconference held between representatives of ARIAD and the FDA on 26 November 2013, it was agreed that the information request would be responded to within PAS-007 because (b) (4) has, at the request of FDA, been withdrawn. A partial response to the 25 November 2013 request for information was included in an amendment submitted on 27 November 2013 (NDA 203469, sequence 0086).

This amendment provides the response to the remaining elements of that 25 November 2013 information request. The components of this submission are described below and were submitted by email to Commander Diane Hanner on 02 December 2013:

- Response to FDA Information Request items 1a and 1b (1.11.3 Efficacy Information Amendment)
- ADVO.xpt and data definition table (define.pdf)
- SAS program for ADVO.xpt

SUBMISSION TECHNICAL SPECIFICATIONS

ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008)*. This submission consists of Module 1 documents. The submission is approximately 2.5 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 02 December 2013.

If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg

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Date: 2013.12.03 09:41:35 -05'00'

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

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04 December 2013

PROPOSED REMS FOR NDA 203469
PRIOR APPROVAL SUPPLEMENT - 008

Robert C. Kane, MD.
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0088

Attn: Ms. Diane Leaman, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This prior approval supplement concerns the New Drug Application (NDA) 203469 for Iclusig® (ponatinib) 15 mg and 45 mg tablets for oral use, submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD). Iclusig was granted accelerated approval on 14 December 2012 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 (TKI) therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior TKI therapy. ARIAD has temporarily suspended marketing of Iclusig while revisions to the US prescribing information (USPI) and medication guide and the implementation of a risk evaluation and mitigation strategy (REMS), the subject of this supplement, are under review by FDA.

Your safety labeling change notification letter dated 25 November 2012 stated that FDA have identified "new safety information" as defined in section 505-1(b)(3) of the Food Drug and Cosmetic Act (FDCA); specifically an increase in frequency of vascular occlusions in patients receiving Iclusig. In the safety labeling change notification letter ARIAD was also informed that, in accordance with section 505-1 of the FDCA, FDA have determined that a REMS is necessary for Iclusig to ensure the benefits of the drug outweighs the risks based on the new safety information described above.

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In this prior approval supplement, ARIAD is proposing a new REMS with a goal to educate prescribers about the serious risks of vascular occlusion. The featured element of the proposed REMS is a communication plan that will be implemented with those healthcare providers who are likely to prescribe Iclusig. This communication plan will consist of the following: Dear Healthcare Provider (DHCP) REMS Introductory Letter; Dear Professional Society (DPS) REMS Introductory Letter; REMS Fact Sheet; Journal Information Piece; and Iclusig REMS Website.

ARIAD will submit REMS Assessments to FDA 1 year, 3 years and 7 years from the date of initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. ARIAD will submit each assessment so that it will be received by the FDA on or before the due date.

SUBMISSION COMPONENTS:
This REMS supplement includes the following components. Each document is provided in PDF and MS Word format.

- Iclusig REMS
- Iclusig REMS Supporting Document
- Dear Healthcare Provider (DHCP) REMS Introductory Letter
- Dear Professional Society (DPS) REMS Introductory Letter
- REMS Fact Sheet
- Journal Information Piece
- Outline for Iclusig REMS Website

SUBMISSION TECHNICAL SPECIFICATIONS
ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008)*. This submission consists of Module 1 documents. The submission is approximately 2.85 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 04 December 2013.

If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg

Digitally signed by Andrew P Slugg
DN: cn=Andrew P Slugg, o=ARIAD Pharmaceuticals, Inc., ou=Regulatory Affairs, email=andrew.slugg@ariad.com, c=US
Date: 2013.12.04 19:53:39 -05'00'

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

26 LANDSDOWNE STREET ● CAMBRIDGE, MA 02139-4234 ● TELEPHONE 617 494 0400 ● FACSIMILIE 617 494 1828

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203469/S-007

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

ARIAD Pharmaceuticals
Attention: Andrew Slugg
Executive Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139-4234

Dear Mr. Andrew Slugg:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 203469

SUPPLEMENT NUMBER: 007

PRODUCT NAME: Iclusig® (ponatinib) 15 mg and 45 mg tablets for oral use

DATE OF SUBMISSION: November 27, 2013

DATE OF RECEIPT: November 27, 2013

This supplemental application was submitted in response to the November 25, 2013, FDA letter which provides for notification of safety labeling changes post-approval REMS, and additional post marketing requirements.

This supplemental application proposes the inclusion of new safety information in the Iclusig labeling, specifically an increase in frequency of vascular occlusions. The following sections of the US Prescribing Information (PI) have been revised:
INDICATIONS AND USAGE, BOXED WARNING, DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS. Your submission also includes a Medication Guide, which reflects this new safety information.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 203469/S-007** submitted on November 27, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIANE C HANNER
12/04/2013

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ARIAD®

12 December 2013

SUPPLEMENT 007
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

Robert C. Kane, MD.
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0089
Submission of FDA Form 3674

Attn: Ms. Diane Leaman, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This amendment concerns the prior approval supplement (PAS-007) proposing safety labeling changes under 505(o)(4) submitted on 27 November 2013 (NDA 203469, sequence 0085) to the New Drug Application (NDA) 203469 for Iclusig® (ponatinib), submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD). Iclusig was granted accelerated approval on 14 December 2012 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 (TKI) therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior TKI therapy. ARIAD has temporarily suspended marketing of Iclusig while revisions to the US prescribing information (USPI) and medication guide and the implementation of a risk evaluation and mitigation strategy (REMS) are under review by FDA.

Please refer to the 04 December 2013 acknowledgement letter for PAS-007 from Commander Diane Hanner. In that letter, ARIAD was requested to submit a certification that all applicable requirements of 42 USC § 282(j) have been met. Therefore, this submission contains the FDA Form 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B)" to accompany PAS S-007.

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SUBMISSION TECHNICAL SPECIFICATIONS

ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008).* This submission consists of Module 1 documents. The submission is approximately 3.25 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 11 December 2013.

If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg

Digitally signed by Andrew P Slugg
DN: cn=Andrew P Slugg, o=ARIAD Pharmaceuticals, Inc., ou=Regulatory Affairs, email=andrew.slugg@ariad.com, c=US
Date: 2013.12.12 08:57:31 -05'00'

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

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MEMORANDUM OF TELECONFERENCE

Teleconference Date: December 16, 2013 2:45 PM – 3:00 PM

Application Number: NDA 203469
Product Name: Iclusig (ponatinib)
Sponsor/Applicant Name: Ariad Pharmaceuticals

Subject: REMS and PMR discussion

FDA Participants

Division of Hematology Products
Ann Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Qin Ryan, MD, PhD, Medical Officer for Safety
Diane Leaman, Safety Project Manager
Angelo de Claro, MD, Clinical Team Leader
Nicole Verdun, MD, Medical Officer
Theresa Carioti, MPH, Regulatory Project Manager

Office of Clinical Pharmacology
Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Jingyu Yu, PhD, Pharmacometrics Reviewer

Office of Biostatistics
Lie Nie, PhD, Statistics Team Leader

Office of Surveillance and Epidemiology/ Division of Risk Management
Cynthia LaCivita, PharmD, Team Leader
Kate Heinrich Oswell, PharmD, Drug Risk Management Analyst
Naomi Redd, PharmD, Drug Risk Management Analyst

Office of Surveillance and Epidemiology/ Division of Pharmacovigilance 2
Peter Waldron, MD, Medical Officer

Office of New Drugs, Immediate Office
Mwango Kashoki, MD, Associate Director for Safety

Office of Compliance
Haley Seymour, MS, Consumer Safety Officer

Office of Regulatory Policy
Nancy Dickinson, PharmD

FDA's Office of Communications
Lindsay Davison, PharmD, Health Promotion Officer

Office of Prescription Drug Promotion
Kathleen Davis, Labeling Reviewer

Sponsor/Applicant Participants
Dan Bollag, PhD, Senior Vice President, Regulatory Affairs and Quality
Tim Clackson, PhD, President, Research and Development
Ron Knickerbocker, PhD, Vice President, Biostatistics and Data Sciences
Maureen Curran, RN, Senior Director, Pharmacovigilance and Risk Management
Andrew Slugg, MS, MBA, Senior Director, Regulatory Affairs

1.0 BACKGROUND:

Iclusig was approved on December 14, 2012 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. At the time of initial approval, the label contained information about the risks of blood clots in the Boxed Warning and Warnings and Precautions sections of the Full Prescribing Information.

Post approval, the Agency became aware of new clinical trial data as well as postmarketing safety reports indicating an increase of arterial and venous occlusions in patients treated with Iclusig. The Agency considered this to be "new safety information" as defined under the Federal Food, Drug, and Cosmetic Act (FDCA). The FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. The Agency issued Drug Safety Communications (DSC) on October 11 and 31, 2013 to convey this new safety finding of the increased risk of occlusive events. Marketing of the drug Iclusig was suspended on October 31, 2013 and the Agency issued a third DSC on November 5, 2013 to inform physicians and patients of an expedited process for obtaining the drug under emergency IND.

On November 25, 2013, the Agency issued a formal communication the provided for safety labeling change requirement, the need for a REMS, and the need for additional Postmarketing requirement studies. Following this communication, the Agency held a Tcon with Ariad on November 26, 2013 to discuss what elements need to be submitted in accordance with the November 25, 2013 letter. That discussion pertained to the REMS, post marketing requirement studies (PMRs), and revisions to the label based on the new safety data.

In response, Ariad submitted a labeling supplement (S-07) on November 27, 2013 and a REMS supplement (S-08) on December 5, 2013.

The purpose of the December 16, 2013, tele-conference was to discuss the outstanding PMRs, provide comments on the pending REMS, and discuss the transition plan for resuming marketing

of Iclusig. Note, there had been previous discussion with Ariad regarding negotiation of the PMRs and milestones during a T-con on December 5, 2013.

2.0 DISCUSSION:

The Agency discussed the comments on the REMS and stated the primary revision to the REMS documents included revisions to the indication: specifically, the removal of the word "(b) (4) when referring to the patient population and replacing it with "revised indications have been limited to". The FDA stated the comments would be forthcoming with revised REMS document and revised REMS supporting document, in tracked-changes. Ariad acknowledged the comment and responded that they accepted the revision.

The Agency further discussed the outstanding PMRs. The Agency previously sent comments and revisions of the PMRs on December 13, 2013. Ariad's response on December 16, 2013 was reviewed. Ariad's revisions included changes to existing PMR 3, PMR 5, and created a new PMR 6.

PMR 3 provides for long-term follow-up of all patients enrolled in the Phase 1 and Phase 2 clinical trials. The Agency stated that Ariad would need to provide a final study report date (rather than an (b) (4) report date). The Agency asked Ariad to indicate reasonable length of follow-up and agreement was reached with date of March/2017.

PMR 5 provides for PK exposure response and dose response data. The Agency had no further comment on PMR 5.

PMR 6 was proposed by Ariad and the Agency accepted this PMR in concept. The Agency proposed some additional language for this PMR.

The FDA's edits/comments delineating the edits of the PMRs is attached to the end of this document.

Lastly, the Agency inquired about Ariad's plans for transitioning Iclusig back into marketing – specifically asking what time is needed to get final printing and supplying the specialty pharmacies. Ariad's reply indicated that assuming an action is taken this week, they will be ready in mid-January 2014. FDA stated the Agency's expectation is that EINDs will continue during the transition period back to marketing in order to provide drug to patients who need it.

Ariad queried if the Agency would be communicating either a press release (PR) or drug safety communication (DSC). The Agency replied that there would be no PR; however, a DSC is planned. The Division advised Ariad if they had specific questions to contact FDA's Office of Communications.

3.0 ACTION ITEMS:

Following the T-con, FDA agreed to provide comments on the revised PMRs and revised REMS documents. See the attached file on the PMR discussion and negotiation.

PMR 3

Provide long-term follow-up of all patients enrolled in the Phase 1 (AP24534-07-101) and Phase 2 (AP24534-10-201) clinical trials. Assess the long-term safety of ponatinib treatment, including the long-term risk of vascular occlusive events. [redacted] - Include narratives for all cases of vascular occlusion. The final [redacted] report submission should include text and data sets. [redacted]

PMR Schedule Milestones:

[redacted] Final Report Submission: [redacted] 03/2017

[redacted]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA A CARIOTI
12/17/2013

Confidential

17 December 2013

SUPPLEMENT 008
PROPOSED REMS AMENDMENT - FINAL REMS

Robert C. Kane, MD
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0091

Attn: Diane Leaman, Regulatory Project Manager
Theresa A. Carioti, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This amendment concerns the prior approval supplement (PAS-008) proposing a risk evaluation and mitigation strategy (REMS) submitted on 04 December 2013 (NDA 203469, sequence 0088) to the New Drug Application (NDA) 203469 for Iclusig® (ponatinib), submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD). Your safety labeling change notification letter dated 25 November 2012 stated that FDA have identified "new safety information" as defined in section 505-1(b)(3) of the Food Drug and Cosmetic Act (FDCA); specifically an increase in frequency of vascular occlusions in patients receiving Iclusig. In the safety labeling change notification letter ARIAD was also informed that, in accordance with section 505-1 of the FDCA, FDA have determined that a REMS is necessary for Iclusig to ensure the benefits of the drug outweighs the risks based on the new safety information described above.

In this supplement, ARIAD has proposed a new REMS with the following goals:

- Inform prescribers of the indications for Iclusig which are limited to:
    - Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

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    - Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
- Inform prescribers of the serious risk of vascular occlusion and thromboembolism associated with Iclusig treatment.

The featured element of the proposed REMS is a communication plan that will be implemented with those healthcare providers who are likely to prescribe Iclusig. This communication plan will consist of the following: Dear Healthcare Provider (DHCP) REMS Introductory Letter (print/email); Dear Professional Society (DPS) REMS Introductory Letter (print/email); REMS Fact Sheet; Journal Information Piece; and Iclusig REMS Website. ARIAD has revised the REMS document and REMS supporting materials to be consistent with the final version of the prescribing information sent to FDA by email on 17 December 2013. The submission components are further described below.

ARIAD will submit REMS assessments to FDA 1 year, 3 years and 7 years from the date of initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. ARIAD will submit each assessment so that it will be received by the FDA on or before the due date.

SUBMISSION COMPONENTS
This amendment to the supplement contains the final and agreed upon components for the REMS.

- Iclusig REMS containing:
    - Dear Healthcare Provider (DHCP) REMS Introductory Letter – Print
    - Dear Healthcare Provider (DHCP) REMS Introductory Letter – Email
    - Dear Professional Society (DPS) REMS Introductory Letter – Print
    - Dear Professional Society (DPS) REMS Introductory Letter – Email
    - REMS Fact Sheet
    - REMS Journal Information Piece
    - REMS Website Landing Page
- Iclusig REMS Supporting Document

SUBMISSION TECHNICAL SPECIFICATIONS
ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008)*. This submission consists of Module 1 documents. The submission is approximately 2.85 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 17 December 2013.

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If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg

Digitally signed by Andrew P Slugg
DN: cn=Andrew P Slugg, o=ARIAD Pharmaceuticals, Inc., ou=Regulatory Affairs, email=andrew.slugg@ariad.com, c=US
Date: 2013.12.17 16:31:27 -05'00'

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

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18 December 2013

SUPPLEMENT 007
SAFETY LABELING CHANGES UNDER 505(o)(4) – AMENDMENT
FINAL PRESCRIBING INFORMATION AND MEDICATION GUIDE
FINAL POSTMARKETING REQUIREMENTS

Robert C. Kane, MD
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0090

Attn: Ms. Theresa A. Carioti, MPH, Regulatory Project Manager
Ms. Diane Leaman, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This amendment concerns the prior approval supplement (PAS-007) proposing safety labeling changes under 505(o)(4) submitted on 27 November 2013 (NDA 203469, sequence 0085) to the New Drug Application (NDA) 203469 for Iclusig® (ponatinib), submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD).

Your safety labeling change notification letter dated 25 November 2012 stated that FDA have identified "new safety information" as defined in section 505-1(b)(3) of the Food Drug and Cosmetic Act; specifically an increase in frequency of vascular occlusions in patients receiving Iclusig. In the safety labeling change notification letter, ARIAD was requested to address this new safety information in the INDICATIONS AND USAGE, BOXED WARNING, DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS sections of the US prescribing information (USPI) and medication guide. Additionally ARIAD was requested to commit to additional post marketing requirements (PMRs) to further evaluate vascular occlusions associated with Iclusig.

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ARIAD has updated the USPI and medication guide addressing all of the changes agreed with FDA including those versions sent by email to on 5 December 2013, 11 December 2013, 12 December 2013, and 17 December 2013. This also includes the final revisions requested of ARIAD on 17 December 2013

This amendment to PAS S-007 also includes the final PMRs. The enclosed list of PMRs incorporates the discussions held between ARIAD and the Agency and represents the company's final proposed PMRs for this supplement.

SUBMISSION COMPONENTS
This prior approval supplement includes the following components:

- Iclusig USPI
- Iclusig Medication Guide
- Final Post Marketing Requirements

SUBMISSION TECHNICAL SPECIFICATIONS
ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008).* This submission consists of Module 1 documents. The submission is approximately 1.75 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 17 December 2013.

If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg

Digitally signed by Andrew P Slugg
DN: cn=Andrew P Slugg, o=ARIAD Pharmaceuticals, Inc., ou=Regulatory Affairs, email=andrew.slugg@ariad.com, c=US
Date: 2013.12.18 09:20:26 -05'00'

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

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From:	Carioti, Theresa
To:	"Andrew P. Slugg"
Bcc:	LaCivita, Cynthia
Subject:	RE: NDA 203469 Iclusig- Final FDA comments on REMS sent 12/17/13
Date:	Tuesday, December 17, 2013 2:36:00 PM
Attachments:	Iclusig Proposed REMS 12-17-13 FINAL.DOCX
Importance:	High

Dear Andrew,
The team has done a final review of all the REMS documents. There is one correction in the REMS document. Please see the attached file in the section about the journal piece where we replaced the word " (b) (4) " with the word "**approved"**.

We have no further comments. Please accept the tracked changes in the REMS supporting document.

In addition, please proceed with making the official submission thru the gateway this afternoon/evening. Please submit the documents in this manner:

1. A final clean version of the REMS and all the REMS materials as one complete document. The RESM document should appear first followed by all the REMS materials in the order they are listed in the REMS.

2. The REMS supporting Document should be submitted as a separate clean file, i.e. without track changes.

Kindly confirm receipt of this email message.

Thank you.

Theresa

From: Andrew P. Slugg [mailto:Andrew.Slugg@ariad.com]
Sent: Tuesday, December 17, 2013 1:32 PM
To: Carioti, Theresa
Subject: RE: NDA 203469 Iclusig- FDA comments on REMS - Clarification re: REMS Supporting document
Importance: High

Dear Theresa,

Thank you for this clarification. We have accepted all of the changes in the REMS document and REMS supporting document and have made three additional very minor edits to the REMS supporting document that will appear in track changes:

1) updated version number and date;
2) updated Table of Contents;

3) deleted (b) (4)

All of the REMS supporting materials (REMS letters – print and email version, REMS Journal Ad, REMS Website, REMS Fact Sheet) have been revised as requested and are attached. Please let me know when we are cleared for the final REMS submission.

Thank you,

Andrew

From: Carioti, Theresa [mailto:Theresa.Carioti@fda.hhs.gov]
Sent: Tuesday, December 17, 2013 11:29 AM
To: Andrew P. Slugg
Subject: RE: NDA 203469 Iclusig- FDA comments on REMS - Clarification re: REMS Supporting document

Dear Andrew,
The feedback I have received from the FDA review team is summarized below.

To clarify, the Agency recommends removal of (b) (4) *from the REMS Supporting Document. After further discussion within the Agency, we believe this text would be better to consider including when you submit your protocol for PMR 1.*

Please send your revised/final REMS document, revised/final REMS supporting document, and all revised REMS materials that incorporates yesterday's comments. Please send today via email first for the team's final review and concurrence.

Thank you,
Theresa

From: Andrew P. Slugg [mailto:Andrew.Slugg@ariad.com]
Sent: Tuesday, December 17, 2013 9:54 AM
To: Carioti, Theresa
Subject: RE: NDA 203469 Iclusig- FDA comments on REMS

Good morning Theresa,

Thank you for the follow-up. We'll be ready to react when we receive your guidance.

Thanks,

Andrew

From: Carioti, Theresa [mailto:Theresa.Carioti@fda.hhs.gov]
Sent: Tuesday, December 17, 2013 9:19 AM
To: Andrew P. Slugg
Subject: RE: NDA 203469 Iclusig- FDA comments on REMS

Hi Andrew,
Thanks for the quick review. I am awaiting guidance from the Division of Risk Management (DRISK) on (b) (4) of the REMS supporting document. I will send you a reply as soon as it's available.

Regards,
Theresa

From: Andrew P. Slugg [mailto:Andrew.Slugg@ariad.com]
Sent: Tuesday, December 17, 2013 7:50 AM
To: Carioti, Theresa
Subject: RE: NDA 203469 Iclusig- FDA comments on REMS

Good Morning Theresa,

We have revised all of the REMS materials and are prepared to send them back with the REMS and REMS supporting documents very quickly. We have no objections to the changes that were made but would like to receive confirmation that we should delete (b) (4) of the REMS supporting document. If so, we will delete (b) (4) that is referenced in the REMS supporting document.

Thank you,

Andrew

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc
26 Landsdowne Street
Cambridge, MA 02139-4234
Mobile: (b) (6)
Office: +1 617 503 7097

From: Carioti, Theresa [mailto:Theresa.Carioti@fda.hhs.gov]
Sent: Monday, December 16, 2013 4:53 PM
To: Andrew P. Slugg
Subject: NDA 203469 Iclusig- FDA comments on REMS
Importance: High

Dear Andrew,
Please refer to NDA 203469 for Iclusig (ponatinib). The FDA team has reviewed the submission sent in earlier this morning and provided the following comments on the REMS.

The REMS and REMS Supporting Document should be revised as per the edits in track changes in

attachments. In addition, the REMS materials will need to be revised as follows to align with the changes in the REMS document.

Journal Information Piece, Fact Sheet, Website

OLD: (b) (4)

FDA REVISED TEXT: The indications have been limited to:

REMS letters to HCPs

OLD: (b) (4)

FDA REVISED TEXT : Revised indications have been limited to:

REMS Letters to Professional Societies

OLD: (b) (4)

FDA REVISED TEXT : Revised indications have been limited to:

Please review and send back revised versions by 4pm EST - Tuesday, December 17th.

Thank you.

Kindly confirm receipt.

Regards,
Theresa

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov
phone: 301-796-2848

Following this page, 3 pages withheld in full - (b)(4), draft labeling/REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA A CARIOTI
12/17/2013

Confidential

18 December 2013

SUPPLEMENT 007
SAFETY LABELING CHANGES UNDER 505(o)(4) – AMENDMENT
GENERAL CORRESPONDENCE

Robert C. Kane, MD
Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA Reference No. 203469
eCTD Sequence No. 0092

Attn: Ms. Theresa A. Carioti, MPH, Regulatory Project Manager
Ms. Diane Leaman, Regulatory Project Manager
Commander Diane Hanner, CDER Senior Program Management Officer

Dear Dr. Kane:

This correspondence concerns the prior approval supplement (PAS-007) proposing safety labeling changes and post-marketing requirements under 505(o)(4) submitted on 27 November 2013 (NDA 203469, sequence 0085) to the New Drug Application (NDA) 203469 for Iclusig® (ponatinib), submitted and maintained by ARIAD Pharmaceuticals, Inc. (ARIAD). I am writing in reference to the teleconference between representatives from ARIAD and FDA that took place on 16 December 2013 regarding the post-marketing requirements that ARIAD has committed to undertake as a part of this supplement (1.6.3 post-marketing requirements, NDA 203469, sequence 0090). During the course of that meeting, ARIAD was requested to provide FDA with a plan for the re-introduction of Iclusig into marketing and commercial distribution. That plan was sent to Ms. Theresa A. Carioti, MPH, Regulatory Project Manager by email on 17 December 2013. The contents of that email capturing ARIAD's plan is captured below. The purpose of this correspondence is to officially submit our launch plan to this supplement.

26 LANDSDOWNE STREET ● CAMBRIDGE, MA 02139-4234 ● TELEPHONE 617 494 0400 ● FACSIMILIE 617 494 1828

ARIAD ATTENDEES TO 16 DECEMBER 2013 TELECONFERENCE:

- Dan Bollag PhD, Senior Vice President, Regulatory Affairs and Quality
- Tim Clackson PhD, President, Research and Development
- Ron Knickerbocker PhD, Vice President, Biostatistics and Data Sciences
- Maureen Curran RN, Senior Director, Pharmacovigilence and Risk Management
- Andrew Slugg MS, MBA, Senior Director, Regulatory Affairs

PLAN FOR THE RE-INTRODUCTION OF ICLUSIG:

Week of 16 December 2013

- FDA Action approving new USPI, Medication Guide, and REMS (baseline assumed)
- www.iclusig.com refreshed with updated prescribing information, medication guide, important safety information, FDA drug safety communication, and information on how to obtain Iclusig during transition
- ARIAD issues Dear Healthcare Provider (DHCP) to inform physicians of revisions to prescribing information, medication guide, and implementation of REMS

Week of 23 December 2013

- Letter sent to all single patient IND (sIND) holders announcing approval of new USPI, Medication Guide and REMS, outlining estimated timing for transitioning sIND to commercial supply

Week of 30 December 2013

- REMS website goes live

Week of 6 January 2014

- REMS letters distributed by email to HCPs and Professional Societies
- Letter sent to all sIND holders outlining transition process for their existing patient(s) from supply under the sIND to commercial supply

Week of 13 January 2014

- Specialty Pharmacy to begin outreach to sIND holders to help facilitate the transition from sIND supply to commercial supply

Week of 20 January 2014

- Resumption of full commercial distribution and sales
- Notification of resumption of full commercial distribution and sales and discontinuation of sIND to all sIND holders
- ARIAD will begin transferring all requests received under sIND to commercial drug supply

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SUBMISSION TECHNICAL SPECIFICATIONS

ARIAD is submitting this amendment to the NDA supplement in electronic CTD (eCTD) format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008)*. This submission consists of Module 1 documents. The submission is approximately 1.39 MB and is certified virus free with Symantec Endpoint Protection, version 12.1.671.4971. The virus definition file was last updated on 18 December 2013.

If you have any questions, please contact Andrew P. Slugg, Senior Director, Regulatory Affairs, by telephone at (617) 503-7097, by facsimile at (617) 225-2688, or by email at andrew.slugg@ariad.com; alternately, contact Bao Le, Manager, Regulatory Affairs, by telephone at (617) 503-7168, by facsimile at (617) 225-2688, or by email at bao.le@ariad.com.

Sincerely,

Andrew P Slugg

Digitally signed by Andrew P Slugg
DN: cn=Andrew P Slugg, o=ARIAD Pharmaceuticals, Inc., ou=Regulatory Affairs, email=andrew.slugg@ariad.com, c=US
Date: 2013.12.18 17:49:27 -05'00'

Andrew P Slugg
Senior Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.

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