REMS Document
Initial Approval 12/2013

NDA 203469

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

ARIAD Pharmaceuticals, Inc.
26 Landsdowne Street
Cambridge, MA 02139
Phone: (617) 494-0400
Fax: (617) 225-2688

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

Reference ID: 3425782

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.

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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

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Iclusig® REMS

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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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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:**

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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
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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

A nonpromotional fact sheet, reviewed by the FDA, with more detailed safety information is available here:
www.iclusigREMS.com

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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)	

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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.

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ICLUSIG®
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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).

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

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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.

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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

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- Treatment of adult patients with chronic phase, accelerated phase, or blast phase CML 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 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.

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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.

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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