

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203469Orig1s000

**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 Management Review

Date: November 27, 2012

Reviewer: Cynthia LaCivita, Pharm.D., Risk Management Analyst Team
Leader, Division of Risk Management (DRISK)
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Drug Name(s): Iclusig (ponatinib)

Therapeutic Class: Tyrosine kinase inhibitor

Dosage and Route: 15 mg and 45 mg; oral tablet

Application Type/Number: NDA 203469

Applicant/sponsor: Ariad Pharmaceuticals. Inc.

OSE RCM #: 2012-2074

1. INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for Iclusig (ponatinib). The applicant did not submit a proposed REMS or risk management plan.

1.1 BACKGROUND

On July 30, 2012, the Division of Hematology Products (DHP) received the initial Rolling Review submission from Arid for Iclusig (ponatinib), new drug application (NDA) 203469. Ponatinib is a novel synthetic orally-active tyrosine kinase inhibitor (TKI) with the proposed indication, for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior TKI therapy.

CML is a myeloproliferative neoplasm characterized by unregulated growth of myeloid cells in the bone marrow, and an increased number of these cells in the blood. CML is associated with a specific chromosomal abnormality, which is a reciprocal translocation of chromosome 9 and 22, known as the Philadelphia chromosome. CML has an incidence of approximately 1-2 cases per 100,000¹ and in 2010 approximately 4870 new cases of CML were diagnosed in the United States.² The Philadelphia chromosome to a lesser extent is also found in ALL.

Currently, there are four TKI approved for the treatment of patients with CML, which target the Bcr-Abl kinase, they are: imatinib (2001), dasatinib (2006), nilotinib (2007), and bosutinib (2012). Unfortunately, many patients will develop resistance to these drugs. In pharmacology studies, ponatinib appears to inhibit multiple kinases including Bcr-Abl kinase and mutant variations of Bcr-Abl, including a mutation which is a threonine-to-isoleucine substitution at position 315 of Abl (T315I) for which no effective therapy currently exists. Effective therapy for patients who have developed resistance to other TKI, specifically T315 would meet an unmet medical need.

2. REGULATORY HISTORY

- On November 20, 2009 ponatinib was granted Orphan Designation for the treatment of CML and for treatment of Philadelphia chromosome-positive Ph+ALL
- On November 30, 2010 ponatinib was granted Fast Track designation for the same proposed indication.
- On July 13, 2012, ponatinib was granted a Rolling Review Material Reviewed
- The sponsor submitted documents to this NDA on the following dates:
 - July 31, 2012 Arid NDA submission

¹ Jabbour E. and Kantarjian H. (2012), Chronic myeloid leukemia:2012 Update on diagnosis, monitoring, and Management. *Am J. Hematol.* 87:1037-1045.

² Chen Y, Wang H, Hagpo K, and Cortes J. Trends in Chronic myeloid leukemia incidence and survival in the United States from 1975-2009. *Leuk Lymphoma* 2012 Nov 2 [Epub ahead of print]

- September 27, 2012 Arid NDA submission
- Clinical Review of Efficacy and Safety in DARRTS November 19, 2012, by R. Angelo de Claro, M.D.
- Pharmacology/Toxicology Review in DARRTS November 19, 2012 by M. Stacey Ricci, M. Eng., Sc.D. and Pedro L. Del Valle, Ph. D.

3. OVERVIEW OF CLINICAL PROGRAM

The pivotal trial used to determine efficacy and safety was study 10-201 (PACE Trial). PACE is a single-arm, open-label, phase 2 trial of ponatinib that evaluated 444 patients with CML or Ph+ ALL with 6 distinct cohorts based on the patients' stage of disease (CP-CML, AP-CML, BP-CML or Ph+ ALL), resistance or intolerance to prior TKIs (dasatinib or nilotinib), or the presence of the T315I mutation. The dosing regimen for ponatinib was 45 mg orally, once daily.

Data from study 07-101, a Phase 1 clinical, dose-escalation study was included in the analysis of safety.

Ariad has initiated an expanded access program, clinical trial (AP24534-12-901 Protocol), in United States, Europe, Australia, Canada, and Singapore. More than 200 patients have been approved to receive ponatinib in this expanded access program.

Key Efficacy Findings. Please refer to the clinical review by Dr. R. Angelo de Claro for the full review on efficacy and safety. The following is a summary of the key findings from Dr. de Claro's review.

<i>Primary endpoint</i>	<i>Cohort</i>	<i>Response (%)</i>
Major Cytogenetic Response	CP-CML with resistance to prior TKI	99/203 (49)
Major Cytogenetic Response	CP-CML presence of the T315I mutation	45/64 (70)
Major Hematological Response	AP-CMP with resistance to prior TKI	36/65 (55)
Major Hematological Response	AP-CML presence of the T315I mutation	7/18 (39)
Major Hematological Response	BP-CML or Ph+ALL with resistance to prior TKI	19/62 (31)
Major Hematological Response	BP-CML or Ph+ALL presence of the T315I mutation	13/32 (41)

Patients were followed for a minimum of 6 months, with a median follow-up of 10 months. The primary endpoint results were supported by duration of response. The median duration of major cytogenetic response was not reached in patients with CP-CML. The major hematological response for patients with AP-CML, BP-CML and Ph+ALL was respectively 9.5 months, 4.7 months and 3.2 months.

Key Safety Findings

Safety issues observed with ponatinib include:

- Arterial thromboembolic events (11% any grade, 7% serious)
 - Arterial thromboembolic events included myocardial infarction, stroke/TIA, and peripheral arterial ischemic events
- Arterial stenosis (5%)
- Hypertension (72%), serious adverse event (2%)
- Hepatotoxicity (55% increased AST or ALT, 8% grade 3-4), 2 cases of fatal acute liver failure
- Pancreatitis (6%), elevated lipase (31%)
- CNS or GI hemorrhage (4%), any bleeding (23%)
- Cardiac failure (6%), pericardial effusion, pleural effusion, or ascites (8%), any fluid retention (22%)
- Myelosuppression

Grade 3 or 4	CP-CML pts=270	AP-CML pts=85	BP-CML pts=62	Ph+ALL pts=32
thrombocytopenia	34	47	44	47
neutropenia	23	47	48	59
anemia	1	4	11	25

- Supraventricular tachyarrhythmias (5%): atrial fibrillation, atrial flutter, atrial tachycardia, supraventricular tachycardia
- QT prolongation (6 cases, no Torsades de Pointes)
- Gastrointestinal perforation (1 case)
- Tumor lysis syndrome (3 cases)
- Thyroid dysfunction (8 pts in study 10-201, and 21 pts in study 07-101 developed treatment –emergent hypothyroidism)
- Proteinuria (27 pt (33%) in study 07-101 developed –treatment emergent proteinuria)

Deaths: Thirteen percent (57/444) of the patients died during the study or with 30 days of treatment. The most common cause of death was due to disease progression (29 pts) followed by infections (10 pts), hemorrhagic events (6 pts), cardiac failure, arrest or infarction (8 pts), multi-organ failure (2 pts) and once each of pyrexia and dehydration
Fetal harm, is likely based on nonclinical data

6. PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

The following proposed Post-Marketing Requirements (PMRs) were communicated to the applicant on November 15, 2012:

- PMR 1: Continue follow-up of patients (on treatment and in protocol defined post treatment follow-up) and submit a final analysis report of Study 10-201 with 24 months of minimum follow-up for each patient. If 24 months of follow-up is not possible for certain patients, provide justification for each patient.
- PMR 2: Submit safety data from one or more randomized controlled trials that isolates the effect of the drug adequately to characterize the safety of Iclusig.
- PMR 3: Assess the QT effect of Iclusig.
- PMR 4: Characterize the effect of Iclusig on platelet function.

- PMR 5: Conduct a dedicated drug interaction trial in humans to determine the effect of coadministration of the strong CYP3A4 inducer rifampin on the pharmacokinetics of ponatinib in healthy subjects.
- PMR 6: Conduct a dedicated hepatic impairment trial in humans to determine the effect of hepatic impairment (i.e., Child-Pugh classes A, B, and C) on the pharmacokinetics of ponatinib when compared to healthy subjects.
- PMR 7: Collect sparse PK from all patients in a clinical trial. Your ongoing trial AP24534-12-301 may be suitable for this objective. Exposure-response analysis should be conducted for both efficacy and safety endpoints. Based on the results of these analyses, a trial to evaluate lower dose or an alternate dosing regimen of ponatinib may be necessary.
- PMR 8: Conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib in healthy subjects.

7. ADVISORY COMMITTEE

None.

8. DISCUSSION

Ponatinib appears to inhibit multiple tyrosine kinases including Bcr-Abl TKI and VEGF-receptor kinases inhibitors. The safety profile of ponatinib is similar to that observed with other Bcr-Abl TKI used to treat CML (Appendix A). Arterial thromboembolic events, gastrointestinal perforations, proteinuria and hypertension are similar to the risks reported with VEGF-receptor kinases and are listed in the warning sections of their respective labels for one or more of the following VEGF-receptor kinase inhibitors: axitinib, bevacizumab, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib.

DRISK does not recommend a REMS for the management of the risks associated with ponatinib for the following reasons: the efficacy of ponatinib was demonstrated in patients with CML or Ph+, ALL resistant or intolerant to prior TKI therapy and if approved could fulfill an unmet medical need; the target population is managed by prescribers who are familiar with this disease and the safety profile of the other approved Bcr-Abl TKI and VEGF-receptor kinases inhibitors. With the exception of nilotinib, the risks associated with the use of the other Bcr-Abl TKI have been addressed through labeling. Nilotinib was approved with a REMS (Medication Guide and communication plan) to mitigate the drug risk of QT prolongation, reduce medication errors involving drug-food interactions and incorrect dosing intervals, and to minimize potential drug-drug and disease-drug interactions. Vandetanib, a VEGF receptor kinase inhibitor was approved with a REMS (MG, CP and ETASU- prescriber and pharmacy certification) to mitigate the risk of QT prolongation /Torsades de pointes/sudden death. There were no cases of Torsades de pointes reported for ponatinib.

DRISK concurs with DHP that the management of the risks associated with treatment of ponatinib can be managed at this time through labeling, postmarketing requirements (PMRs) are necessary to further assess and characterize the risks. The product label will include a

boxed warning to communicate the risks of arterial thrombosis and hepatotoxicity with ponatinib.

9. CONCLUSION

DRISK concurs with the DHP and recommends that, based on the available data and the potential benefits and risks of treatment, a REMS is not required for ponatinib and the risks associated with ponatinib can be managed through labeling. If new safety information becomes available this decision can be re-evaluated.

Appendix A
Comparison of NMEs Imatinib, Sprycel, Tasigna, and Bosulif

Established & (Trade Name)	imatinib (GLEEVEC)	dasatinib (SPRYCEL)	nilotinib (TASIGNA)	bosutinib monohydrate (BOSULIF)
NDA/ (Applicant)/ Approval date	NDA 021335; NDA 021588 (Novartis) 2001	NDA 021986; 022072 (BMS) 2006	NDA 022068 (Novartis) 2007	NDA 203341 (Wyeth) 2012
Class	protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase	Multi-tyrosine kinase inhibitor	Second generation inhibitor of Bcr-Abl tyrosine kinase	tyrosine kinase inhibitor; third drug in the class
Orphan Designation	01/31/2001 for treatment of CML	11/18/2005 for treatment of Ph+ ALL leukemia 11/28/2005 for treatment of CML	4/27/2006 for treatment of patients with CML	02/24/2009 for the treatment of CML
Risk Management	No risk management measures beyond labeling	No risk management measures beyond labeling	REMS: Medication Guide and Communication Plan	No risk management measures beyond labeling
Labeling				
Box Warning	n/a	n/a	QT Prolongation (Sudden Death) Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome Avoid concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors Avoid food 2 hours before and 1 hour after taking dose	n/a
Warning & Precautions	<ul style="list-style-type: none"> • Fluid Retention and Edema • Hematologic Toxicity • Severe Congestive Heart Failure and Left Ventricular Dysfunction • Hepatotoxicity • Hemorrhage • Gastrointestinal Disorders • Hypereosinophilic Cardiac Toxicity • Dermatologic Toxicities • Hypothyroidism • Toxicities from Long-Term Use • Use in Pregnancy • Children and Adolescents • Tumor Lysis Syndrome • Driving and Using Machinery 	<ul style="list-style-type: none"> • Myelosuppression • Bleeding Related Events (mostly associated with severe thrombocytopenia) • Fluid Retention • QT Prolongation • Congestive Heart Failure, Left Ventricular Dysfunction and Myocardial Infarction • Pulmonary Arterial Hypertension (PAH) • Use in Pregnancy 	<ul style="list-style-type: none"> • Myelosuppression • QT Prolongation • Sudden Deaths • Elevated Serum Lipase • Hepatotoxicity • Electrolyte Abnormalities • Drug Interactions • Food Effects • Hepatic Impairment • Tumor Lysis Syndrome • Total Gastrectomy • Lactose • Monitoring Laboratory Tests • Use in Pregnancy 	<ul style="list-style-type: none"> • Gastrointestinal toxicity • Myelosuppression • Hepatic toxicity • Fluid Retention • Embryoal toxicity
Pregnancy Category	D	D	D	D

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/s/

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11/28/2012

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