CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203469Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	203469
Applicant Name	Ariad Pharmaceuticals, Inc.
Date of Submission	9/27/12
PDUFA Goal Date	3/27/12
Proprietary Name / **Established (USAN) Name**	Iclusig/ponatinib
Dosage Forms / Strength	15 mg and 45 mg round, white, film-coated tablets
Applicant's Proposed Indication(s)	For the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy
Action/Recommended Action for NME:	Approval (Accelerated)

Material Reviewed/Consulted OND Action Package, including:	
Division Director	Ann Farrell, MD
Medical Officer Review	R. Angelo DeClaro, MD/Virgina Kwitkowski, MS/RN/ACBP-NP
Statistical Review	Kyung Y Lee, PhD/Mark Rothmann, PhD
Pharmacology Toxicology Review	Pedro Del Valle, PhD/Stacey Ricci, MSc/ Haleh Saber, PhD
CMC Review/OBP Review	Donghao (Robert) Lu, PhD/Amit K. Mitra, PhD/Nallaperum Chidambaram, PhD
Microbiology Review	Steven P. Donald, MS/Bryan S. Riley, PhD
Clinical Pharmacology Review	Joseph Grillo, PharmD/Rachelle M. Lubin, PharmD/ Julie Bullock, PharmD
DDMAC	Gina McKnight-Smith/Kathleen Davis
DSI	Anthony Orencia, MD and Susan Thompson, MD
CDTL Reviews	Virgina Kwitkowski, MS/RN/ACBP-NP
OSE/DMEPA	Sarah K. Vee, PharmD/Yelena Maslov, PharmD/Carol Holquist, RPh

1. Introduction

On September 27, 2012, Ariad Pharmaceuticals submitted a new molecular entity for ponatinib, an oral tyrosine kinase inhibitor (TKI) for the proposed indication of "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 tyrosine kinase inhibitor therapy."

The applicant has submitted this application for accelerated approval relying primarily on a single phase 2 trial enrolling patients with CML or ALL in different stages of disease.

Ponatinib is not approved in any other country.

2. CMC/Device

There are no issues that preclude approval of this application from a CMC perspective. CMC reviewers state:

The ponatinib hydrochloride drug product is recommended for APPROVAL from the standpoint of chemistry, manufacturing and controls. Include the following language in the action letter: Based on the provided stability data, an expiration dating period of 12 months is granted for the drug product when stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

Inspections are complete and did not identify any issues that would preclude approval. Please see action letter for CMC PMC.

3. Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval of this application from a Nonclinical perspective. From Dr. Saber's review:

[Ponatinib] has activity against BCR-ABL and multiple mutant forms of BCR-ABL, including the T315I mutation. Ponatinib also inhibits several other kinases, including VEGFRs, FGFRs, PDGFRs, RET, KIT, FLT3, and SRC family members. Ponatinib showed anti-tumor activity in mice bearing tumor xenografts expressing native BCRABL or the T315I mutant. The pharmacologic class assigned to ponatinib is "kinase inhibitor" consistent with other drugs of the same class, such as imatinib, dasatinib, nilotinib, and bosutinib.

Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in in vitro systems and/or in animal species. Animal toxicology studies were conducted in appropriate species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Ponatinib-related toxicities in rats and monkeys included: lymphoid depletion, necrosis involving the exocrine pancreas with low incidence lipase elevation, and elevated liver enzymes (ALT and AST). Cardiovascular findings in animals included systolic heart murmurs and myocardial necrosis; however, these findings were of low incidence and/or non-dose-dependent. In patients treated with ICLUSIG, serious safety concerns include the findings in the cardiovascular, hepatic and pancreatic systems.

Ponatinib was not mutagenic or clastogenic when tested in the battery of genotoxicity studies. At a maternally toxic dose of 3 mg/kg/day, ponatinib was teratogenic when administered to pregnant rats during the period of organogenesis. Systemic exposure in animals at this dose was equivalent to that reported for patients treated with the recommended ponatinib dose (45 mg/day). Ponatinib also caused embryofetal toxicities in rats at systemic exposures below those observed in patients treated with the recommended dose. A pregnancy category D has been assigned to this drug. Due to the teratogenicity findings in rats, an embryofetal developmental study in a second species was deemed not necessary.

Fertility studies using ponatinib have not been conducted; however, based on findings in the reproductive organs in the general toxicology studies, ponatinib may impair male and female fertility. Findings in animals included: degeneration of epithelium of the testes and follicular atresia in ovary and associated endometrial atrophy.

4. Clinical Pharmacology/Biopharmaceutics

There are no issues that preclude approval of this application from a Clinical Pharmacology perspective. However, there are several PMRs that will be included in the action letter.

The recommended dose is 45 mg per day with or without food. Peak concentrations are observed within 6 hours after oral administration. Ponatinib is highly plasma protein bound *in vitro*. CYP3A4 and (to a lesser extent) CYP2C8, CYP2D6 and CYP3A5 are involved in metabolism of ponatinib *in vitro*. Dose modification is suggested for those who will take ponatinib with a strong CYP3A4 inhibitor. Ponatinib has not been studied in patients with hepatic or renal impairment. However hepatic impairment is a major route of excretion for ponatinib.

5. Clinical Microbiology

The product microbiology review did not identify any issues that would preclude approval.

6. Clinical/Statistical-Efficacy

The applicant submitted results from a multicenter, international, single-arm clinical trial (PACE) of 449 patients with disease that was resistant or intolerant to prior tyrosine kinase inhibitor therapy. The primary endpoints were Major Cytogenetic Response (MCyR) for patients with CP-CML and Major Hematologic Response (MaHR) for patients with AP-CML, BP-CML or Ph+ALL. FDA required that the sponsor commit to submit 24-month follow-up data for all patients as a condition for the accelerated approval.

The efficacy results demonstrated a 54% MCyR rate in patients with CP-CML. Seventy percent of patients with CP-CML with T315I mutation achieved MCyR. The median duration of MCyR had not yet been reached at the time of analysis. For patients with AP-CML, BP-CML and Ph+ ALL, the MaHR rates were 52%, 31% and 41%, respectively. The median duration of MaHR in patients with AP-CML, BP-CML and Ph+ ALL was 9.5 months, 4.7 months and 3.2 months respectively.

7. Safety

The safety population of Study 10-201 consisted of 449 patients. A summary of key safety findings from Dr. DeClaro's review are listed below:

- *The major safety issues identified include: 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 cardiovascular safety profile for Iclusig is notable for arterial ischemic events and hypertension. Based on the July 23, 2012 updated data cut-off date, 8% of patients experienced serious ischemic events. Arterial thromboembolic events and hypertension have been reported with other kinase inhibitors that inhibit VEGF-receptor kinase activity.*

Labeling for ponatinib will include a Boxed Warning alerting patients and healthcare professionals that arterial thrombosis and liver toxicity have occurred in Iclusig-treated patients. The most common side effects reported in the clinical trial include hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, fever, joint pain, and nausea.

At the time of completion of Dr. DeClaro's review, the clinical team determined the need for the following PMRs (1) submission of 2-year follow-up efficacy and safety results for Study 10-201 and (2) submission of the safety results from a randomized clinical trial that isolates the treatment effect of ponatinib. See action letter for these PMRs.

8. Advisory Committee Meeting

This product was not taken to an Oncologic Drugs Advisory Committee (ODAC) because other TKIs have been approved for the treatment of CML based on single arm response data and the clinical study design was acceptable. Additionally, similar applications with trials using the same endpoints were not taken to ODAC.

9. Pediatrics

This product has Orphan drug designation, therefore, PREA does not apply.

10. Other Relevant Regulatory Issues

There are no other relevant unresolved regulatory issues.

11. Labeling

The labeling was reviewed by all disciplines and consultant staff.

12. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action: Accelerated Approval.

- Risk Benefit Assessment
  The risk benefit assessment suggests that ponatinib is effective for the indication sought by the applicant. Responses including CCyR were observed in the cohorts. Serious cardiovascular and thromboembolic adverse events were observed in the single arm trial. Although the applicant presented information suggesting that the majority of patients who had cardiovascular complications on ponatinib had a previous history of cardiovascular risk factors, the single arm trial design does not permit the Agency to state with assurance that ponatinib did not contribute to the adverse events observed. Thus the labeling will include most of these serious adverse events in the warnings and precautions section. This information will allow prescribers to make decisions about whether individual patients should receive ponatinib treatment.

  Additional longer term safety and efficacy information will be provided with 24 months of follow-up from the ongoing single arm trial with multiple cohorts used for the accelerated approval decision, AP24534-10-201. Because it is not possible to isolate from a single arm trial whether the adverse event profile seen is due to ponatinib or the presence of underlying cardiovascular risk factors, we will request submission of 12 months of safety data from an ongoing randomized trial, AP24534-12-301, comparing ponatinib with imatinib in patients who are newly diagnosed with CML.

  The risk benefit profile, which was also discussed by Dr. Farrell, Ms. Kwitkowski and Dr. DeClaro, is acceptable. In addition, the review team recommends approval of this NDA, and I concur.

- Recommendation for Post marketing Risk Management Activities
  Routine post-marketing surveillance and submission of safety information from their ongoing single arm trial with multiple cohorts (AP24534-10-201) and provide 12 months of safety follow up data from the ongoing randomized controlled trial (AP24534-12-301).

- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)
  See Action letter.

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/s/

TAMY E KIM
12/14/2012

RICHARD PAZDUR
12/14/2012