CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203469Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

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

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Ariad Pharmaceuticals has submitted a new molecular entity NDA for ponatinib, an oral tyrosine kinase inhibitor (TKI). The applicant's proposed indication is "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 tyrosine kinase inhibitor therapy."

Ponatinib is not approved in any country or region.

2. Background

The applicant has submitted an application for accelerated approval primarily relying on a single phase 2 trial enrolling patients with CML or ALL in different stages of disease. The applicant submitted the application as a rolling review. The application was complete as of September 27, 2012.

3. CMC/Device

Drs. Lu, Mitra, and Chidambaram reviewed this supplement. In their review they state the following:

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).

The following post approval agreement was negotiated with the applicant.

ARIAD will submit the updated method "Identification, Content Uniformity, Assay and Impurities Method for Ponatinib (AP24534) Tablets, 15mg and 45 mg" (AM1281) post approval, minimally within 3 months, to the application via a Supplement, Changes Being Effected – 30 Days (CBE-30).

Inspections are complete and did not identify any issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

From Dr. Saber's review:

Ponatinib is a small molecule tyrosine kinase inhibitor developed for the treatment of CML. It 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.

5. Clinical Pharmacology/Biopharmaceutics

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 CYP 3A4 inhibitor. Ponatinib

has not been studied in patients with hepatic or renal impairment. However hepatic impairment is a major route of excretion for ponatinib.

There are no issues which would preclude approval of ponatinib based on the clinical pharmacology reviews. However, the clinical pharmacology review team recommends the following post-marketing commitment and requirements (text is from the review):

Commitment

Evaluate the in vitro potential for the displacement of ponatinib, at a therapeutic concentration, from its protein binding sites in human plasma following addition of frequently used, highly protein-bound co-medications (e.g., warfarin, salicylic acid, ibuprofen, propranolol, glibenclamide, digitoxin, phenytoin, and nifedipine) at therapeutic or at supratherapeutic concentrations. Positive findings from this in vitro study may require additional trials in vivo.

Requirements

1. Conduct a dedicated drug interaction trial in humans to determine the effect of coadminstration of the strong CYP3A4 inducer rifampin on the pharmacokinetics of ponatinib in healthy subjects.

2. 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.

3. Conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib in healthy subjects.

4. Collect sparse PK in your ongoing trial AP24534-12-301 from all patients. Exposure- response analysis should be conducted for both efficacy and safety endpoints. Based on the results of these analyses, you may be required to conduct a trial to evaluate lower dose or an alternate dosing regimen of ponatinib.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

The applicant submitted results from a single Phase 2 clinical trial. Study AP24534-10-201 or 10-201, is a single-arm, international clinical trial where the efficacy and safety of

Iclusig was studied in cohorts of patients with CML (all phases) or Ph+ ALL.

From the executive summary of Dr. DeClaro's review:

Clinical Benefit. *The efficacy of Iclusig was evaluated in 444 patients enrolled in 6 cohorts according to disease type and presence of T315I mutation. A summary of the key efficacy findings based on the data cut-off date of April 27, 2012 (6 months minimum follow-up for all patients, 10 months median follow-up) are listed below:*

- *The primary endpoint for patients with CP-CML was Major Cytogenetic Response (MCyR). The MCyR rate was 54% (144/267) overall in patients with CP-CML; 49% (99/203) in the resistant cohort and 70% (45/64) in the T315I cohort.*
- *The primary endpoint for patients with AP-CML was Major Hematologic Response (MaHR). The MaHR rate was 52% (43/83) overall in patients with APCML; 55% (36/65) in the resistant cohort and 39% (7/18) in the T315I cohort.*
- *The primary endpoint for patients with BP-CML or Ph+ALL was also MaHR. The MaHR rate was 31% (19/62) in patients with BP-CML and 41% (13/32) in patients with Ph+ ALL.*
- *The primary endpoint results were supported by duration of response. In patients with CML, the median duration of MCyR was not reached. For patients with AP-CML, BP-CML, and Ph+ ALL, the median duration of MaHR were 9.5, 4.7, and 3.2 months respectively.*

I concur with the conclusions of the clinical and statistical review teams regarding the demonstrations of efficacy for the indications. Additionally ponatinib appears to be very effective for those patients with CML whose disease has developed a mutation known as T315I. The presence of the T315I “gatekeeper” mutation has been associated with resistance to currently approved TKIs including imatinib, dasatinib, and nilotinib.

8. Safety

From the executive summary of Dr. DeClaro’s review:

Risk. *The safety population of Study 10-201 consisted of 449 patients. A summary of the key safety findings 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.*

- *The ponatinib dose was 45 mg PO once daily. The median exposure duration was 9 months for patients with CP-CML or AP-CML, and 3 months for patients with BP-CML or Ph+ALL.*
- *Seventy-three percent of patients required a dose modification due to adverse events. The most common adverse events that lead to dose modification include thrombocytopenia, neutropenia, lipase elevation, rash, abdominal pain, pancreatitis, and elevated liver enzymes.*
- *The 120-day safety update submission (data cut-off date July 23, 2012) was notable for the following: increase in frequency of arterial thromboembolic events compared to the original submission, and two cases of fatal acute hepatic failure.*

Dr. DeClaro concluded in his review the following:

At the time of completion of this review, the clinical team determined the need for the following post-marketing requirements: (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. The reader is referred to the action letter and secondary reviews for the final list of postmarketing requirements.

I concur with the conclusions of the clinical and statistical review teams. The identified safety issues from the single arm trial raise concern. The applicant did present information suggesting that the majority of patients who had cardiovascular complications on ponatinib had a previous history of cardiovascular risk factors. However, 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. In addition two PMRs (see list below in section13) will provide additional safety information.

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 the ongoing randomized trial, AP24534-12-301, comparing ponatinib with imatinib in patients who are newly diagnosed with chronic myelogenous leukemia.

9. Advisory Committee Meeting

This product was not taken to an Oncologic Drugs Advisory Committee because the Office of Hematology and Oncology Products and the Division of Hematology Products have approved other TKIs for the treatment of CML. The clinical design was

acceptable and similar applications using the same endpoints were not taken to an Advisory Committee meeting.

10. Pediatrics

Orphan drug designation

11. Other Relevant Regulatory Issues

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

Financial Disclosures were reviewed and did not appear to impact the integrity of the application.

Office of Scientific Investigation (DSI)
The OSI review did not find the data unreliable in support of the application.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  Accelerated Approval for patients with chronic phase, accelerated phase, blast phase, or Philadelphia chromosome positive acute lymphoblastic leukemia resistant/or demonstrated intolerance to prior tyrosine kinase inhibitor therapy

- 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 the ongoing randomized trial, AP24534-12-301, comparing ponatinib with imatinib in patients who are newly diagnosed with chronic myelogenous leukemia.

- 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). See commitments below.

- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)

We have asked the applicant:

to provide 24 months efficacy and safety data from the ongoing single arm trial (AP24534-10-201)

to provide a 12 month safety update from their randomized controlled trial (AP24534-12-301)

to further assess the QT effect of ponatinib

to characterize the effect of ponatinib on platelet function

to conduct a dedicated drug interaction trial in humans to determine the effect of coadminstration of the strong CYP3A4 inducer rifampin on the pharmacokinetics of ponatinib in healthy subjects.

to 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

to conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib in healthy subjects.

to collect sparse PK in your ongoing trial AP24534-12-301 from all patients. Exposure- response analysis should be conducted for both efficacy and safety endpoints.

to submit update information regarding assays for impurities

to evaluate the in vitro potential for the displacement of ponatinib, at a therapeutic concentration, from its protein binding sites in human plasma following addition of frequently used, highly protein-bound co-

medications (e.g., warfarin, salicylic acid, ibuprofen, propranolol, glibenclamide, digitoxin, phenytoin, and nifedipine) at therapeutic or at supratherapeutic concentrations.

For final versions of the PMRs and PMC see the approval letter.

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
12/13/2012