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RESEARCH**

APPLICATION NUMBER:

203341Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	203341
Supplement #	
Applicant Name	Wyeth Pharmaceuticals, Inc.
Date of Submission	11/17/11
PDUFA Goal Date	09/17/12
Proprietary Name / Established (USAN) Name	Bosulif/Bosutinib
Dosage Forms / Strength	Oral tablets/100 mg and 500 mg
Proposed Indication(s)	For the treatment of patients with chronic myelogenous leukemia (chronic phase, accelerated phase and blast phase) with resistance or intolerance to prior therapy
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Division Director	Ann Farrell, MD
Medical Officer Review	Karen McGinn MSN, CRNP/ Virginia Kwitkowski MS, RN, ACNP-BC
Regulatory Project Manager	Diane Hanner
Statistical Review	Kallappa Koti Ph.D./Mark Rothmann, PhD
Pharmacology Toxicology Review	Shwu Luan Lee PhD/Haleh Saber, PhD
CMC Review/OBP Review/Biopharmaceutics	Joyce Crich, PhD/Janice Brown, MS/Akm Khairuzzaman, PhD/Angelica Dorantes, PhD
Microbiology Review	Robert Mello, PhD/John Metcalfe, PhD
Clinical Pharmacology Review	Elimika Pfuma, PhD/Justin Earp, PhD/Bahru Habtemariam PhD/Rosane Charlab Orbach, PhD
DDMAC	
DSI	Anthony Orenca, MD/Janice K. Pohlman, MD/Susan D Thompson, MD
CDTL Reviews	Virginia Kwitkoswki CRNP
OSE/DMEPA	
OSE/Epidemiology	
OSE/DRISK	
Other - IRT	Venkatesh Bhattaram/Nitin Mehrotra/Moh Jee Ng/Joanne Zhang/ Monica L Fiszman/Norman Stockbridge
Other – Pediatrics & Maternal Health Team Other- Pharmacometrics	

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

1. Introduction & Background

On November 17, 2011, Wyeth submitted this NDA for bosutinib, an oral tyrosine kinase inhibitor, for the treatment of chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy. Bosutinib is not marketed in the United States or in any other country.

There are multiple approved products to treat CML in the chronic, accelerated or blast phases of the disease. See table below for information on the recently approved indications for CML.

Table 1. FDA Approved Tyrosine Kinase Inhibitor Drugs for Chronic Myelogenous Leukemia

Drug	Indication
Imatinib	<ul style="list-style-type: none">• Adults with newly diagnosed Philadelphia positive (Ph+) chronic phase (CP) CML• Adults with Ph+ CP CML after failure of interferon alpha therapy• Children with newly diagnosed Ph+ CP CML• Patients with Ph+ CML in blast crisis, (BC) accelerated phase (AP), or in chronic phase after failure of interferon-alpha therapy
Dasatinib	<ul style="list-style-type: none">• Newly diagnosed adults with Ph+ CML in CP• Adults with CP, AP, myeloid blast phase, lymphoid blast phase, Ph+ CML with resistance or intolerance to prior therapy including imatinib• Adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy
Nilotinib	<ul style="list-style-type: none">• Newly diagnosed adult patients with Ph+ CML in CP• CP and AP CML in adult patients resistant to or intolerant to prior therapy that included imatinib

Reviewer's Table

Prior to the approval of the oral tyrosine kinase inhibitors, drug and biologic product treatment for CML included interferon, ara-c, hydroxyurea, busulfan, and other chemotherapy regimens. Prior to the development of tyrosine kinase inhibitors, stem cell transplant was the only hope for long term disease control. With the emergence of the tyrosine kinase inhibitor therapies, long term disease control can be achieved without stem cell transplant.

2. CMC/Device

CMC reviews state the following:

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA...

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product bosutinib tablets (100 mg and 500 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

The Office of Compliance has issued an overall "acceptable" recommendation on May 10, 2012 for all facilities.

3. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues that preclude approval. Nonclinical reviewers indicate in their reviews that bosutinib is not genotoxic nor mutagenic nor is there any evidence that bosutinib is carcinogenic.

Dr. Saber's TL memo states:

I concur with Dr. Lee that from a nonclinical perspective, BOSULIF may be approved for the proposed indication. No additional nonclinical studies are needed to support approval of BOSULIF for the proposed indication.

4. Clinical Pharmacology/Biopharmaceutics

The primary review of the Clinical Pharmacology review states:

Bosutinib exhibits approximately linear PK in the dose range of 200 – 800 mg. No exposure response relationships for effectiveness or safety were observed at the dose of 500 mg. In a food-effect trial, a high-fat meal increased bosutinib exposure 2-fold. Bosutinib showed better tolerability when co-administered with food; as a result bosutinib was co-administered with food in patient trials. Bosutinib is primarily metabolized by CYP3A4. Clinical trials showed that the strong CYP3A4 inhibitor ketoconazole increased bosutinib AUC 9-fold while the strong CYP3A4 inducer rifampin decreased bosutinib AUC by 94%. A 2-fold increase in exposures was observed in patients with hepatic impairment. In a thorough QT trial, bosutinib did not cause significant changes in placebo adjusted, baseline-corrected QTc....

The IRT review stated that administration of BOSULIF at a recommended dose of 500 mg with food does not prolong the QT interval and co-administration with ketoconazole also did not prolong the QT interval.

The clinical pharmacology review team recommends the following post-marketing requirement:

Requirement

1) Conduct a drug-drug interaction trial to evaluate the effect of a moderate CYP3A4 inhibitor (e.g. erythromycin) on the pharmacokinetics of bosutinib. The proposed protocol must be submitted for review prior to trial initiation.

5. Clinical Microbiology

There are no outstanding microbiology issues that preclude approval.

6. Clinical/Statistical-Efficacy

The primary trial supporting this NDA is Trial 200, which was a single-arm, open-label, multi-center trial enrolling 546 patients with either chronic phase (CP), accelerated phase (AP) or blast phase (BP) CML previously treated with at least one prior tyrosine kinase inhibitor (TKI). All patients received prior imatinib therapy. In the total patient population, 73% were imatinib resistant and 27% were imatinib intolerant. In this trial, 53% of patients were males, 65% were Caucasian, and 20% were 65 years old or older. The efficacy endpoints for patients with CP CML were the rate of major cytogenetic response (MCyR) at week 24 and the duration of MCyR. The efficacy endpoints for patients with AP or BP CML were the rate of confirmed complete hematologic response (CHR) and overall hematologic response by week 48.

The following table outlines the trial design for the trials that were submitted within this NDA. Trial 3000 was a failed trial that did not demonstrate the superiority of bosutinib over imatinib in the newly diagnosed setting. Dasatinib and nilotinib have suggested superiority over imatinib in the newly diagnosed setting and have received accelerated approval on that basis.

Table 2. Tables of Clinical Trials (Reviewer Table)

Trial	Trial Design	Treatment Groups (N)	Endpoint
200	Phase 1/2 open-label, 2-part trial in subjects with Ph+ leukemia	<ul style="list-style-type: none"> CP CML Second line (288) and Third line (118) AP CML (144); Ph+ ALL (24) 	MCyR @ week 24 CHR by week 48
3000	Phase 3 RCT in subjects with newly diagnosed CP-CML to compare bosutinib to imatinib	<ul style="list-style-type: none"> CP CML treated with bosutinib (248) CP CML treated with imatinib (251) 	CCyR @ 1 year CCyR @ 1 year
2203	Phase 1/2 open-label trial in subjects with Ph+ leukemia	<ul style="list-style-type: none"> Phase 1 (17) Phase 2 (35) 	MTD MCyR and CHR

The following text is from the primary clinical reviewer's Executive Summary:

This reviewer recommends regular approval of Bosulif (bosutinib) for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance to, or intolerance of prior therapy. The Applicant has provided clinical evidence of activity for bosutinib in patients with CML in second and later lines of treatment and an acceptable risk profile. The pivotal trial was a Phase 2, single arm trial which required all subjects to have previously been treated with imatinib. The trial enrolled 288 patients with Chronic Phase (CP) CML in second line treatment with bosutinib. Of the 288 patients, 200 were resistant to imatinib, and 88 were intolerant of imatinib. The primary endpoint of the trial was major cytogenetic response (MCyR) at 24 weeks in patients with CP CML who were resistant to imatinib. The trial also enrolled patients with CP CML who had been exposed to more than one tyrosine kinase inhibitor (TKI) and patients in advanced phases of CML which includes accelerated phase (AP) and blast phase (BP) and enrolled a small cohort of patients with Ph+ acute lymphoblastic leukemia (ALL). Key secondary endpoints were MCyR at 24 weeks in patients with CP CML who were intolerant of imatinib in second line treatment with bosutinib; MCyR by 24 weeks in patients with third line CP CML, and objective hematologic response (OHR) by 48 weeks in patients with AP CML, BP CML and Ph+ ALL.

The MCyR rate for patients with CP CML who were imatinib resistant and were in second line treatment with bosutinib at 24 weeks was 35.5% (95% CI: 29, 42). The Kaplan-Meier estimate of maintaining MCyR at Year 1 and Year 2 was 68.4% (95% CI: 58, 77) for both years in the imatinib-resistant cohort.

The MCyR rate for patients with CP CML who were imatinib intolerant and were in second line treatment with bosutinib at 24 weeks was 30% (95% CI: 20, 40). The Kaplan-Meier estimate of maintaining MCyR at Year 1 and Year 2 was 88% (95% CI: 71, 95) for both years in the imatinib-intolerant cohort.

The MCyR rate for patients with CP CML who were in third line treatment with bosutinib following prior treatment with imatinib and dasatinib or imatinib and nilotinib by week 24 was 27% (95% CI: 19, 36). The Kaplan-Meier estimate of maintaining MCyR was 63.9% (95% CI: [44, 78) at Year 1 and 59% (95% CI: 39, 75) at Year 2.

The confirmed OHR rate by week 48 in patients with AP CML and prior therapy with more than one TKI (AP multi TKI) was 43% (95%CI: 26, 63) with a median duration of 42 weeks. Confirmed CHR rate in the same cohort was 27% (95% CI: 11, 42) with a median duration of 74 weeks. The confirmed OHR rate by week 48 in patients with AP CML and prior imatinib only was 64% (95% CI: 47, 79) with a median duration of 53 weeks. The confirmed CHR rate by week 48 in the same cohort was 41% (95% CI: 26, 56) with a median duration of 69 weeks.

The confirmed OHR rate by week 48 in patients with BP CML and prior therapy with more than one TKI (BP multi TKI) was 19% (95% CI: 6, 38) with a median duration of 31 weeks. Confirmed CHR in the same cohort was 4%

(95% CI: 0, 20) with a duration of 28 weeks. The confirmed OHR rate by week 48 in patients with BP CML and prior imatinib only was 36%(95% CI: 20, 55) with a median duration of 29 weeks. Confirmed CHR rate in the same cohort was 24% (95% CI: 10, 39) with a median duration of 26 weeks.

Only 2 of 24 patients with Ph+ ALL responded, and the Applicant discontinued enrollment of this cohort after the first interim analysis. Because the population of patients with Ph+ ALL was small in this trial, and because there were few responders in this cohort, the Sponsor did not seek an indication and the results will not be reflected in labeling.

The statistical team confirmed the applicant's findings. Here is language from Dr. Koti's review:

Except the imatinib-resistant cohort analysis in Study 3160A4-200-WW, all other cohorts' analyses were either exploratory or indicated inefficacy or were based on small samples. Efficacy results from cohorts other than imatinib-resistant cohort should not be used to support labeling claims...

In this reviewer's opinion, the collective evidence does not support the approval of this application as a whole.

Dr. Farrell disagrees with the interpretation that efficacy was not demonstrated in the "intolerant" population as conveyed in her Summary review. Dr. Farrell states:

Patients with CML who were intolerant to other therapies had durable responses with bosutinib. In the absence of treatment, patients with CML who were intolerant to other therapies would be expected to have a 0% response rate.

Drs. Rothmann and Sridhara did not concur with Dr. Koti's recommendation. In their memo they concluded:

Based on the size of the response rates and the durability of the responses across CML cohorts, it clear how a conclusion or recommendation can be made for approval and labeling claims for all cohorts except the Ph+ ALL cohort (which had a 0% MCyR rate at 24 weeks).

The review team requests longer follow-up data (2 years) from the ongoing 200 trial.

7. Safety

The safety database was adequate for analysis. Similar safety findings for other approved TKIs were observed with bosutinib. These findings were myelosuppression, gastrointestinal, fluid retention (peripheral edema, pleural and cardiac effusions), constitutional (fatigue) and hepatotoxicity. The major serious safety findings associated with bosutinib use were: NCI CTCAE grade 3 and 4 hematologic and diarrhea, pneumonia and rash.

Myelosuppression, gastrointestinal, hepatic toxicity, and fluid retention are in the warnings section of the labeling.

Anaphylaxis

Two cases of anaphylactic shock were observed in clinical trials. Prior episodes of hypersensitivity are mentioned as a contraindication to continued use.

8. Advisory Committee Meeting

This product was not taken to an Oncologic Drugs Advisory Committee Meeting since multiple other tyrosine kinase inhibitors using the same primary efficacy endpoint for use in the treatment of CML and with similar safety concerns have been approved.

9. Pediatrics

This application has Orphan drug designation and is therefore exempt from PREA requirements.

10. Other Relevant Regulatory Issues

DSI inspection of requested sites did not reveal any unreliable data or study misconduct.

11. Labeling

There are no unresolved issues that preclude approval.

12. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action: Approval

- Risk Benefit Assessment

The risk benefit assessment suggests that bosutinib is effective for the treatment as stated in the indication. The treatment was tolerated with the side effect profile observed similar to other TKIs. The most common side effects were hematologic, gastrointestinal, dermatologic, and fatigue. The Risk benefit profile, which was also discussed by Dr. Farrell, Ms. Kwitkowski and McGinn, is acceptable. In addition, the review team recommends approval of this NDA, and I concur.

- Recommendation for Post marketing Risk Management Activities

A REMS is not Recommended. Routine post-marketing surveillance is recommended.

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

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

/s/

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08/31/2012

RICHARD PAZDUR
08/31/2012