CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203585Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	203585
Applicant Name	IVAX International GMBH/Teva (US Agent)/Cephalon, Inc.
Date of Submission	03/30/12
PDUFA Goal Date	01/30/13
Proprietary Name / **Established (USAN) Name**	Synribo/Omacetaxine mepesuccinate
Dosage Forms / Strength	8 mL clear glass single-use vial containing 3.5 mg of omacetaxine mepesuccinate for injection
Proposed Indication(s)	for the treatment of adult patients with chronic or accelerated phase chronic myelogenous leukemia (CML) with resistance or intolerance to prior tyrosine kinase inhibitor therapy (TKI) including imatinib, dasatinib, or nilotinib
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Division Director	Ann Farrell, MD
RPM	Theresa Ferrara
Medical Officer Review	Firoozeh Alvandi, MD/Virginia Kwitkowski, CRNP
Statistical Review	Chia Wen Ko, PhD/Mark Rothmann, PhD
Pharmacology Toxicology Review	Tim Kropp, PhD/Stacy Ricci MS/Haleh Saber, PhD
CMC Review/OBP Review	Debasis Ghosh, PhD/Nallaperum Chidambaram, PhD/Elsbeth Chikdale PhD/Richard Lostritto, PhD
Microbiology Review	Erika Pfeiler, PhD/Bryan S Riley, PhD
Clinical Pharmacology Review	Joseph Grillo, PharmD/Bahru Habtermariam, PharmD/Jee Eun Lee, PhD/Kevin Krudys, PhD/Elsbeth Chikhale, PhD/Julie Bullock, PhD
DDMAC	Gina McKnight-Smith/Karen Rulli
DSI	
CDTL Reviews	Virginia Kwitkowski, CRNP
OSE/DMEPA	
OSE/Epidemiology	
OSE/DRISK	
Other - statistical safety	
Other – Pediatrics/ Maternal Health Team	

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

1. Introduction

Teva/Cephalon submitted this NDA for omacetaxine mepesuccinate (homoharringtonine) on March 30, 2012, for the treatment of adult patients with chronic or accelerated phase chronic myelogenous leukemia (CML) with resistance or intolerance to prior tyrosine kinase inhibitor therapy (TKI) including imatinib, dasatinib, or nilotinib.

Omacetaxine mepesuccinate does not have approval in the EMA.

2. CMC

There are no issues precluding approval from a CMC perspective. The CMC review states:

The NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An 'Overall Acceptable' site recommendation from the Office of Compliance has been made. From the CMC perspective, this NDA is recommended for approval pending the satisfactory resolution of the labeling issues….

Based on the submission, for omacetaxine mepesuccinate for injection, the shelf-life of 18 months when stored at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) and protected from light can be granted.

3. Nonclinical Pharmacology/Toxicology

Drs. Kropp, Ricci and Saber reviewed this application and did not identify any issues that would preclude approval.

4. Clinical Pharmacology/Biopharmaceutics

There are no issues precluding approval from a clinical pharmacology perspective. The clinical pharmacology review states: *Study CGX-635-205 is the only applicant-sponsored clinical pharmacology study to evaluate single- and multiple-dose PK as well as QTc interval prolongation of omacetaxine in 21 cancer patients. Peak concentrations of omacetaxine are reached 0.5-1 hour after SC injection of Omacetaxine. Omacetaxine has a mean ± SD steady-state volume of distribution of approximately 141±93.4 L following SC administration for 11 days. The plasma protein binding of omacetaxine is less than or equal to 50%. Omacetaxine is primarily hydrolyzed to the inactive 4'-DMHHT metabolite via plasma esterases with little hepatic microsomal oxidative and/or esterase-mediated metabolism in vitro. The major elimination route of omacetaxine is unknown, but will be evaluated post-market. The mean percentage of omacetaxine excreted unchanged in the urine is less than 15%. The mean half-life of omacetaxine and 4'-DMHHT following SC administration is approximately 6 hours and 16 hrs, respectively. The plasma AUC of DMHHT is approximately 13% of omacetaxine AUC. Compared to a single dose, the plasma exposure to omacetaxine at steady state increased 90% following SC injection BID. Interpatient variability in omacetaxine AUC was 70%.*

Omacetaxine is a substrate of P-glycoprotein (P-gp). Omacetaxine and 4'-DMHHT do not inhibit major cytochrome P-450 enzymes (CYPs) or P-glycoprotein (P-gp). The likelihood of Omacetaxine or 4'-DMHHT to induce CYP450 enzymes has not been determined conclusively.

No substantial QT-prolonging effects of omacetaxine were detected. However, QTc effects less than 10 ms could not be verified in the absence of placebo and positive controls.

See action letter for Clinical Pharmacology PMRs.

5. Clinical Microbiology

Drs. Pfeiler and Riley reviewed this application and did not identify any product microbiology issues that would preclude approval.

6. Clinical/Statistical-Efficacy

This application is supported by combined data from two open label single-arm trials enrolling patients with CML in chronic phase (CML-CP) or in accelerated phase (CML-AP). The efficacy population included 76 patients with CML-CP and 35 patients with CML-AP who had received two or more prior TKIs, including imatinib. Major cytogenetic response (MCyR) and Major Hematologic Response (MaHR) were the primary endpoints for CML-CP and CML-AP, respectively. MCyR was achieved in 18.4% of patients with CML-CP (median response duration 12.5 months). MaHR was achieved in 14.3% of patients with CML-AP (median response duration 4.7 months). From Dr. Alvandi's primary review:

Based upon my review of the data submitted in support of this NDA, the recommended regulatory action is accelerated approval of omacetaxine mepesuccinate (subsequently referred to in this review as omacetaxine) as third line therapy for the treatment of accelerated or chronic phase chronic myelogenous leukemia (CML), by subcutaneous route of administration. Accelerated, and not regular, approval is recommended as the applicant has not provided the requisite 24 months of follow-up data that FDA expects for regular approval. The submission contained a median of 19.5 (range 14.4-23.1) and 11.5 (range 6.8-16) months of follow up data for the primary endpoints for CML-CP and CML-AP population, respectively. The recommendation for approval (accelerated) is based upon the results of the analysis of a subset of patients with CML-AP and CMLCP from two trials (for efficacy) CML-202 and CML-203, titled 'Analysis CML-300' and, for the safety analysis includes an additional trial CML4.2/4.3 in patients with CML-AP. These trials were single arm trials conducted in patients who have been intolerant or resistant to at least 2 prior TKIs, one of which must have been imatinib. The subset of patients selected from CML-202 and CML-300 for post hoc efficacy analysis (Analysis CML-300) consists of patients in both trials who received 2 or more approved tyrosine kinase inhibitors (TKIs) at a minimum, had evidence of resistance or intolerance to dasatinib and/or nilotinib.

The efficacy result for the primary endpoint of Major Cytogenetic Response (MCyR) (complete and partial cytogenetic response) for patients with CML-CP was 20.5% with median duration of response of 17.7 months (95% CI 4.1- N/A). Two patients with CML-CP had MCyR at trial entry. With removal of these patients from the efficacy analysis who had MCyR at trial entry, the primary end point of MCyR for patients with CML-CP was 18.4% with a median duration of 12.5 months (95% CI 3.5-NA).

The efficacy result for the primary endpoint of Major Hematologic Response (MaHR) (complete hematologic response and no evidence of leukemia) patients with CML-AP was 26.8% (14.2-42.9) with median duration of 9.0 months (3.6-14.1). Of the CML-CP patients in analysis 300, 24 patients (29.1%) entered the trial in a complete hematologic response (CHR). Of the CML-AP patients in analysis 300, 9 patients (22%) were in CHR at baseline. With removal of those patients from the efficacy analysis who had best response at trial entry, the primary end point of MaHR for patients with CML-AP was 14.3% with a median duration of 4.7 months (95% CI 3.6-NA). The efficacy results from this post-hoc subset analysis of two single-arm trials are adequate given the absence of any approved drug in the third line setting for treatment of CML.

7. Safety

Safety data were evaluated in 163 patients comprised of 108 patients with CML-CP and 55 patients with CML-AP who received at least one dose of omacetaxine mepesuccinate and an additional 4 patients with CML-CP from another open label, single arm trial. The most common (≥20%) grade 1-4 adverse reactions in the combined safety population of patients with CML-CP and AP included thrombocytopenia, anemia, neutropenia, diarrhea,

nausea, fatigue, asthenia, injection site reaction, pyrexia, infection and lymphopenia. The most common (≥5%) grade 3-4 adverse reactions were thrombocytopenia, anemia, neutropenia, febrile neutropenia, asthenia/fatigue, pyrexia and diarrhea.

The most common serious adverse events (reported in ≥ 3 patients) were thrombocytopenia, anemia, neutropenia, febrile neutropenia, pyrexia, diarrhea, pneumonia, cerebral hemorrhage, gastrointestinal hemorrhage and sepsis. Ten deaths were reported within 30 days of the last omacetaxine mepesuccinate dose. Four of these were attributed to progressive disease, four to cerebral hemorrhage, one to multi-organ failure and one to unknown causes.

8. Advisory Committee Meeting

Prior to the submission of NDA 203585, the applicant submitted NDA 22374, which was presented at the Oncologic Drugs Advisory Committee (ODAC) on March 22, 2010. The ODAC discussion focused on the lack of a companion diagnostic to identify the trial population/intended patient population with the Bcr-Abl T315I mutation (for the trial and after approval). The question posed to ODAC was: "*Should a well characterized in vitro diagnostic to identify patients with the T315I mutation be required and reviewed by the FDA and correlated to clinical trial results prior to approval of omacetaxine for the proposed indication?*" The committee vote was 7 "*Yes*" to 1 "No".

NDA 203585 was not taken to ODAC because the Applicant decided to forgo pursuing an indication for CML associated with a T315I Bcr-Abl mutation and the division has approved other agents to treat CML based on single arm response data using the same response criteria. The patient population represents an indication where there is no approved therapy.

9. Pediatrics

Orphan designation, therefore PREA does not apply.

10. Other Relevant Regulatory Issues

There are no unresolved relevant 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 Synribo is effective for the treatment of patients with CML-CP or AP with resistance and/or intolerance to two or more tyrosine kinase inhibitors. There are no other drugs approved for this indication, and this indication represents a relatively refractory patient population. The trial design (single-arm), endpoints used, and use of accelerated approval awaiting more mature data is consistent with prior approval of TKI's for the treatment of CML over the past decade. The most common side effects seen were myelosuppression (thrombocytopenia, neutropenia and anemia), gastrointestinal (diarrhea, nausea) and general (fatigue/asthenia,

pyrexia). The risk benefit profile, which was also discussed by Dr. Farrell, Ms. Kwitkowski and Dr. Alvandi, 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.

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

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/s/

TAMY E KIM
10/25/2012

RICHARD PAZDUR
10/25/2012