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RESEARCH**

APPLICATION NUMBER:

203585Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA #	203585
Supplement #	
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:	
Medical Officer Review	Firoozeh Alvandi, M.D./Virginia Kwitkowski, CRNP
Statistical Review	Chia Wen Ko, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Tim Kropp, Ph.D./Stacy Ricci MS./Haleh Saber, Ph.D.
CMC Review/OBP Review	Debasis Ghosh, Ph.D./Nallaperum Chidambaram, Ph.D./Sarah Miksinski-Pope, Ph.D./Elsbeth Chikdale Ph.D./Richard Lostritto, Ph.D.
Microbiology Review	Erika Pfeiler, Ph.D./Bryan S. Riley, Ph.D.
Clinical Pharmacology Review	Joseph Grillo, Pharm.D./Bahru Habtermariam, Pharm.D./Jee Eun Lee, Ph.D./Kevin Krudys, Ph.D./Elsbeth Chikhale, Ph.D./Julie Bullock, Ph.D.
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
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Signatory Authority Review Template

1. Introduction

On March 30, 2012, Teva/Cephalon submitted this NDA for omacetaxine mepesuccinate (homoharringtonine) 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. Prior to this submission, the applicant submitted NDA 22374 for omacetaxine mepesuccinate (homoharringtonine) for the treatment of adult patients with chronic myeloid leukemia who have failed prior therapy with imatinib, and have the Bcr-Abl T315I mutation. On April 8, 2010, Cephalon received a complete response (CR) letter for NDA 22374 which outlined clinical, clinical pharmacology, nonclinical and product quality issues.

Subsequently the applicant met with the Agency several times to discuss the issues that prompted their CR letter.

Omacetaxine mepesuccinate does not have approval in the EMA. On December 1, 2011, ChemGenex withdrew the marketing application in the EMA.

2. Background

After receiving the CR letter, Cephalon revised its development plan and decided to forgo pursuing an indication for the treatment of adult patients with CML who have the Bcr-Abl T315I mutation. In addition, the applicant addressed the deficiencies cited in the prior CR letter.

3. CMC/Device

Drs. Ghosh and Chidambaram reviewed this application as well as Dr. Miksinski-Pope. In their reviews they state the following:

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.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

The following text is from Dr. Grillo's review:

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 \pm SD steady-state volume of distribution of approximately 141 \pm 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.

There are no issues which would preclude approval of omacetaxine based on the clinical pharmacology reviews. However, the clinical pharmacology review team recommends the following requirements from their second cycle review:

Requirements

- 1) Conduct a Phase 1/2 single arm clinical trial to investigate the pharmacokinetic, safety, and preliminary efficacy of omacetaxine following fixed dose administration in patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) who have failed two or more TKI therapies
- 2) Conduct a mass balance trial in humans to determine the disposition and elimination pathways as well as to characterize the major metabolites of omacetaxine following subcutaneous injection.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

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. This analysis was agreed to by the FDA after the initial application received a CR letter.*

I concur with the conclusions of the clinical and statistical review teams regarding the demonstrations of efficacy for both indications.

8. Safety

From Dr. Alvandi's safety review:

The most frequently reported adverse reactions ($\geq 20\%$) associated with subcutaneous omacetaxine use include thrombocytopenia, anemia, diarrhea, nausea, fatigue/asthenia, febrile neutropenia, and pyrexia.

I concur with the conclusions of the clinical and statistical review teams.

9. Advisory Committee Meeting

From Dr. Alvandi's review:

NDA 22374 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".

This submission was not taken to an Oncologic Drugs Advisory Committee 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.

10. Pediatrics

Orphan designation

11. Other Relevant Regulatory Issues

Financial Disclosures were reviewed and payments to Dr. Cortes and Douer do not appear to have impacted the trial results.

Office of Scientific Investigation (DSI)

From Dr. Alvandi's review:

However, based on prior inspection of clinical sites (during review of NDA 22347), OSI has determined that data from sites 22 and 30 are not reliable and are not to be used in the Agency's analyses of safety and efficacy. Per the August 04, 2010 EMA Inspection Report Tekinex Prof. Hochhaus (inv. site 030), "...important data concerning efficacy (hematologic response) and safety (hematotoxicity) were not collected from the sites. Thus, these relevant data were not provided to the Data Monitoring Committee (DMC), which evaluated the hematologic response (primary efficacy criterion), nor were they taken into account for the evaluation of safety, especially with regard to hematotoxicity. Thus these instructions are not considered adequate. This relevant issue was also discussed with the sponsor. Furthermore, the instructions in section 8.6 of the clinical trial protocol: The principal investigator should continue to report any significant followup information to the sponsor up to the point the event has resolved" are not precise enough to ensure complete collection of efficacy and safety data, especially in relation to the primary efficacy endpoint. Results of unscheduled laboratory tests were only in a few cases entered in the CRF and reported. Several laboratory results which were considered significant and AE related (fulfilling the clinical trial protocol criteria) were not entered in the CRF by the site."

Conclusion

While OSI uncovered issues for two of the sites, the other sites appeared reliable. Thus the data from the two unreliable sites were not used for a regulatory decision.

PMR/PMCs

The applicant is being requested to address 3 major issues as post-marketing requirements (PMRs) : 1) longer term efficacy and safety, 2) assess fixed dosing as an alternative to current BSA based dosing and 3) understand mass balance in humans.

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
- Risk Benefit Assessment

The risk benefit assessment suggests that Synribo is effective for the treatment of patients with CML-CP or AP based on preliminary data (response rate). The most common side effects seen were myelosuppression (thrombocytopenia, neutropenia and anemia), gastrointestinal (diarrhea, nausea) and general (fatigue/asthenia, pyrexia).

- Recommendation for Post marketing Risk Management Activities -
Routine post-marketing surveillance
- Recommendation for other Post marketing Study Requirements (PMR)/
Commitments (PMC)
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We have asked the applicant to agree to these Post-Marketing Requirements:

PMR-1 -- to continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of CGX-635-CML-300 with 24 months of minimum follow-up data for each patient. If 24 months of follow-up is not possible for certain patients, justification should be provided.

PMR-2 -- to conduct a Phase 1/2 single arm clinical trial to investigate the pharmacokinetic, safety, and preliminary efficacy of omacetaxine following fixed dose administration in patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) who have failed TKI therapy.

PMR-3 – to conduct a mass balance trial in humans to determine the disposition and elimination pathways as well as to characterize the major metabolites of omacetaxine following subcutaneous injection. Depending on the results, hepatic and/or renal impairment trials may be required.

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
10/25/2012