CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203585Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Management Review

Date:	September 18, 2012
Reviewer:	Cynthia LaCivita, Pharm.D. Risk Management Analyst, Team Leader Division of Risk Management (DRISK) Mary Dempsey, B.S. Risk Management Programs, DRISK
Division Director	Claudia Manzo, Pharm D. DRISK
Drug Name(s):	Omacetaxine mepesuccinate
Therapeutic Class:	Cephalotaxine
Dosage and Route:	Lyophilized powder for injection 3.5 mg/vial
Application Type/Number:	NDA 203585
Applicant/sponsor:	Ivax International GmbH (IVAX); US Agent is Teva Branded Pharmaceutical Products R&D, Inc.
OSE RCM #:	2012- 1167

1. INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) omacetaxine mepesuccinate. On March 30, 2012, the Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP), received a new drug application (NDA) 203585 for omacetaxine mepesuccinate. The proposed indication is for treatment of chronic myeloid leukemia (CML), chronic or accelerated phase (CP, AP) resistant or intolerant to prior tyrosine kinase inhibitors (TKI) including imatinib, dasatinib or nilotinib. The compound, cephalotaxine, 4-methyl (2R)-2- hydroxy-2-(4-hydroxy-4- methylpentyl) butanedioate (ester), is a protein synthesis inhibitor lyophilized powder for injection and the current applicant is Ivax International GmbH (IVAX). The sponsor did not submit a proposed REMS or a risk management plan.

2. BACKGROUND

Omacetaxine mepesuccinate for injection, a first-in-class cephalotaxine obtained via semi-synthesis from *Cephalotaxus sp*., is a preservative-free, white to off-white lyophilized powder in a single-use vial containing 3.5 mg omacetaxine mepesuccinate (active ingredient) and mannitol. The proposed indication is for the treatment of adult patients with chronic or accelerated phase CML with resistance or intolerance to prior TKI including imatinib, dasatinib, or nilotinib. The proposed dose and schedule is 1.25 mg/m^2 as a subcutaneous injection twice daily for 14 consecutive days every 28 days (induction cycle), and maintenance treatment with the same dose and twice daily schedule for 7 consecutive days every 28 days.

3. REGULATORY HISTORY

Omacetaxine mepesuccinate received Orphan Product Designation for CML on March 10, 2006. ChemGenex Pharmaceuticals, Inc., initially submitted NDA 022374 on September 8, 2009 and received a Complete Response (CR) letter April 8, 2010; the efficacy trial was a single, small, incomplete trial and 1/3 of patients in the clinical trial were ineligible per protocol-defined. ChemGenex was subsequently acquired by Cephalon in 2011 and NDA 023374 was withdrawn February 7, 2011. Cephalon addressed the CR deficiencies and submitted omacetaxine mepesuccinate as NDA 203585 March 30, 2012.

On August 21, 2012 Cephalon was acquired by Teva Pharmaceutical Industries Ltd., which is now known as Teva Branded Pharmaceutical Products R&D, Inc. The new applicant for NDA 203585 is Ivax International GmbH (IVAX) and the U.S. Agent is Teva Branded Pharmaceutical Products R&D, Inc.

4. MATERIAL REVIEWED

- March 22, 2010 Oncology Drugs Advisory Committee (ODAC) meeting minutes
- April 8, 2010 CR Letter
- March 30, 2012 NDA 203585 CR submission by Cephalon, omacetaxine mepesucicnate, summary of clinical efficacy and integrated summary of safety
- July 31, 2012 Teleconference Meeting minutes, in DARRTS August 2, 2012

- August 15, 2012 submission to revise labeling [redacted] (b) (4)
- August 21, 2012 Sponsor name change
- August 29, 2012 Midcycle slides and presentations by Drs. Firoozeh Alvandi (Clinical Reviewer), Chia-Wen Ko (Statistics) and Stacey Ricci (Pharm/Tox)
- September 18, 2012 sequence 0030, [redacted] (b) (4)

5. REVIEW FINDINGS

5.1 OVERVIEW OF THE CLINICAL PROGRAM

Studies CGX-635-CML-202 (CML-202) (n= 103) and CGX-635-CML-203 (CML-203) (n= 100) were international, multicenter, open-label, single-arm trials used to evaluate the efficacy and safety of omacetaxine in patients with CML in chronic, accelerated and blast phase disease. In study CML-202, patients were required to have T3151 Bcr-Abl gene mutation and failed imatinib treatment. In study CML-203, patients were required to have failed/ intolerant to two TKI. Omacetaxine was administered as a 1.25 mg/m^2 subcutaneous injection twice daily for 14 consecutive days every 28 days (induction cycle), responding patients received maintenance treatment with the same dose and twice daily schedule for 7 consecutive days every 28 days. The number of days that patients received drug treatment was adjusted for patients experiencing myelosuppression. Patients were allowed to continue to receive maintenance treatment for up to 24 months, continuing treatment beyond that was a decision left to the sponsor and investigator based on expected or continued benefit to the patient.

Study CGS-635-CML-300 (CML-300) (n=119) is a subset analysis of CML-202 and CML-203 was used to evaluate the efficacy of omacetaxine. Patients with blast phase disease were excluded from this analysis along with patients who had only failed one TKI, and patients with undocumented resistance or intolerance. An additional 3 patients were excluded from the FDA analysis due to data unreliability.

Key Efficacy Findings

Primary efficacy finding included a major cytogenetic response in 20.5% (16/78) of patients with CML-CP with median duration of 17.7 months; a major hematological response in 26.8% (11/41) of the patients with CML-AP with a median duration of 9.0 months.

Eliminating two patients with CML-CP and that had a cytogentic response at study entry and 6 patients with CML-AP that had a hematologic response at study entry changed the values to 18.4% (14/76) of patients with CML-CP as having a major cytogenetic response with median duration of 12.5 months; and 14.3% (5/35) of the patients with CML-AP as having a major hematological response with a median duration of 4.7 months.

Median follow-up times for the patients in the CML-300 analysis were 19.5 months for the patients with CP-CML and 11.5 months for the patients with AP-CML.

Key Safety Findings

CML-202, CML-203 and CML-04.2/04.3 (total n= 163; CML-CP 108 pts and CML-AP 55 pts) were used to evaluate the safety of omacetaxine.

- *Hematological/Myleosuppression* - NCI CTC Grade 3-4 hematological toxicities in patients with CML-CP and CML-AP included:
  - Thrombocytopenia - 66% CML-CP; 46% CML-AP; the occurrence of grade 4 thrombocytopenia increased the risk of hemorrhage.
  - Anemia - 35% CML-CP; 33% CML-AP
  - Neutropenia - 45% CML-CP; 18% CML-AP
- *Hyperglycemia* –Grade 3/4 12%
- *Injection site erythema* - occurred in 16% of patients; however none were reported as greater than grade 2 toxicity.
- *Gastrointestional*- diarrhea, nausea, constipation, vomiting, stomatitis
- *Potential for embro/ fetal toxicity* –based on pharmacology/toxicity findings
  - Genotoxicity: Omacetaxine was negative in the Ames assay and *in vivo* mouse micronucleus assay; however it was positive in the chromosomal aberration assay in the Chinese Hamster Ovary (CHO). The chromosomal aberration assay is useful in identifying potential mutagens and carcinogens.
  - Reproductive and Developmental Toxicology*:* Dr. Stacey Ricci's slides at the midcycle meeting highlighted that at ½ of the recommended human dose, omacetaxine in mice caused embryo-lethality, decreased bone ossification and decreased fetal body weight.

Reasons for discontinuing treatment included; death (13 pts), progression of disease (51 pts), and lack of efficacy (25 pts). All cause of death, including deaths greater than 30 days from the last dose included cerebral hemorrhage (4), pancytopenia (2), pulmonary hemorrhage (2), sepsis (2) and one each of the following cardiac arrest, neutopenic fever, failure to thrive, liver failure and complications of allergeneic bone marrow transplant.

Other Safety Concerns

(b) (4)

Reviewer Comments: (b) (4)

The agency believed that the preparation of this drug should

follow usual standards for preparing hazardous drugs and sterile drug preparation in an appropriate facility.

On August 15, 2012 the sponsor amended their submission (b) (4) . On September 18, 2012 the sponsor notified the agency acknowledging that (b) (4) . Omacetaxine should be administered to patients in a facility that could reconstitute the drug product in an appropriate manner.

Reviewer Comments: The agency agrees with the sponsor's changes.

5.3 AC STATUS

Omacetaxine, NDA 022374, applicant ChenGenex Pharmaceuticals, was presented to ODAC March 22, 2010 to discuss the clinical significance of the overall response rate and duration of response as well as the benefit:risk ratio for omacetaxine treatment in patients with chronic myeloid leukemia who have failed prior therapy with imatinib, and have Bcr-Abl T315I mutation. The AC Committee voted 7 to 1 in favor of requiring ChemGenex to submit "a well characterized" *in vitro* diagnostic to identify patients with T315I mutations prior to the approval of omacetaxine.

On April 8, 2010 ChenGenex received a Complete Response (CR) that identified the deficiencies requiring correction before resubmission of the application. In 2011, ChenGenex, was acquired by Cephalon, and on February 7, 2011 the FDA acknowledged the withdrawal of NDA 022374. On March 30, 2012 Cephalon submitted new NDA 203585 that addressed the CR deficiencies. At the May 10, 2012 filing meeting, the review team determined that it was not necessary to go to ODAC for this review cycle.

5.4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

The agency is currently working on developing post marketing requirements that include:

- A 24 month follow-up to the pivotal trials to collect data to support converting from accelerated approval to regular approval.
- An open-label study to investigate the pharmacokinetics (absorption, distribution, metabolism, and excretion) of omacetaxine mepesuccinate and metabolites (i.e., 4′-DMHHT and cephalotaxine), following subcutaneous administration of [^{14}C]omacetaxine mepesuccinate in patients with relapsed and/or refractory hematologic malignancies or advanced solid tumors.
- 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.
- A study to explore optimal dosing regimen by evaluating exposure and efficacy with a fixed dosing regimen

6. DISCUSSION

The safety profile of omacetaxine is based on single-arm studies in patients who have failed/intolerant to 2 TKIs. Based on the available data myleosuppression appears to be the most serious adverse event. In the clinical trials this was managed by delaying or decreasing the number of days of treatment. Although, omacetaxine is not a TKI, its adverse event profile was compared to other agents that are approved for the treatment of CML. Treatment with imatinib, dasatinib, and nilotinib (see appendix A) are all associated with hematological toxicity which is addressed through labeling. In general, the adverse effect profile for TKIs also includes gastrointestinal toxicities, fluid retention, and QT prolongation. Of the three previously mentioned agents, nilotinib is only one approved with a REMS, however the REMS is to mitigate the risk of QT prolongation, this risk was not identified with omacetaxine. Bosutinib, a TKI, recently received approval on September 4, 2012, it safety findings are similar to the other TKIs. Bosutinib risks are addressed through labeling.

Based on the available data and in comparison to other approved products for the treatment of CML the risks associated with omacetaxine treatment can be adequately addressed through labeling.

7. CONCLUSION

DRISK concurs with the Division of Hematology Products and recommends that based on the available data and the potential benefits and risks of treatment, a Risk Evaluation and Mitigation Strategy is not required for omacetaxine, the risks associated with omacetaxine can be managed through labeling. If new safety information becomes available this decision can be re-evaluated.

Appendix A
Comparison of Imatinib, dasatinib and nilotinib

Established & (Trade Name)	**Imatinib (GLEEVEC)** NDA 021335; NDA 021588 (Novartis)	**Dasatinib (SPRYCEL)** NDA 021986; 022072 (BMS)	**Nilotinib (TASIGNA)** NDA 022068 (Novartis)
FDA Approval Date	05/10/2001 for NDA 021335 (capsules) Accelerated Approval 50 and 100 mg capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy 02/01/2002 for NDA 021335 (capsules) Accelerated Approval for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) 12/20/2002 for NDA 021335 (capsules) For 100mg capsules for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia 04/18/2003 for NDA 021588 (tablets) Accelerated Approval 100 mg and 400 mg tablets for all indications previously approved as accelerated approval for the tablets 05/20/2003 for NDA 021335 (capsules); 021588 (tablet) Capsules discontinued; Approval tablets for treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy 12/08/2003 NDA 021558 Conversion from Accelerated Approval to regular approval for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy 05/19/2005 new dosage strength, film coated divisible 400 mg tablet	06/28/2006 for NDA 021986 Accelerated Approval for the treatment of adults with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib 06/28/2006 for NDA 022072 regular approval for the treatment of Ph+ ALL 11/08/2007 for NDA 021986 Accelerated Approval for the use of a lower dose for the treatment of adults with chronic phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate 05/30/2008 for NDA 021986 & NDA 022072 new tablet strength, 100 mg film-coated tablets. 05/21/2009 for NDA 021986 Accelerated Approval for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib and the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. 10/28/2010 for NDA 021986 Accelerated Approval for treatment of newly diagnosed adults with chronic myeloid leukemia (CML) in chronic phase	10/29/2007 Accelerated Approval oral capsules for chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included Gleevec® (imatinib) 3/15/2010 Initial REMS approval REMS is Medication Guide, Communication Plan, Timetable for Submission of Assessments 06/17/2010 Accelerated Approval for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase REMS modification to revise Medication Guide which includes the addition of a new indication and language regarding total gastrectomy and revised educational materials that are part of the communication plan 01/14/2011 conversion of accelerated approval to regular approval for chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included Gleevec (imatinib) REMS modification to revise Medication Guide and Communication Plan with new information including updated dosing information concerning mixing the contents of the capsules with applesauce 10/26/2011 revisions to package insert to incorporate treatment-emergent tumor lysis syndrome, to incorporate revised labeling from an interim analysis of a required post-marketing study, to include labeling regarding treatment-emergent peripheral arterial occlusive disease. REMS modification to include Medication Guide revisions to incorporate treatment-emergent tumor lysis syndrome

Established & (Trade Name)	**Imatinib (GLEEVEC)** NDA 021335; NDA 021588 (Novartis)	**Dasatinib (SPRYCEL)** NDA 021986; 022072 (BMS)	**Nilotinib (TASIGNA)** NDA 022068 (Novartis)
	09/27/2006 for the use of Gleevec for newly diagnosed Philadelphia positive CML in pediatric patients 10/19/2006 for the treatment of adult dermafibrosarcoma protuberans (DFSP); for the treatment of adult myelodysplastic syndrome/myeloproliferative diseases (MDS/MPD); for the treatment of adult adult Ph+ acute lymphoblastic leukemia (ALL) monotherapy; for the treatment of adult aggressive systemic mastocytosis (ASM); for the treatment of adult hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL) 09/26/2008 conversion from accelerated approval to regular approval for patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (confirmatory studies) 12/19/2008 Accelerated Approval for the adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive gastrointestinal stromal tumors (GIST). 05/27/2009 conversion from accelerated approval to regular approval for treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in the chronic phase. 04/01/2011 conversion from accelerated approval to regular approval for newly diagnosed pediatric Ph+ CML 01/31/2012 conversion from accelerated approval to full approval of the indication for adjuvant treatment of adult patients following complete resection of Kit (CD117) positive gastrointestinal stromal tumors (GIST) and provides updated Gleevec prescribing information.		11/18/2011 revisions to the package insert to incorporate peripheral arterial occlusive disease and update on study results REMS modification includes minor editorial revisions to the Patient Medication Guide Brochure artwork
Class	protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase	Multi-tyrosine kinase inhibitor	Second generation inhibitor of Bcr-Abl tyrosine kinase
Target	protein-tyrosine kinase inhibitor, designed specific inhibitor of the Bcr-Abl tyrosine kinase	Inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN, c-KIT, EPHA2, and PDGFRß	Inhibitor of tyrosine kinases including BCR-ABL

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Indication	• Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase • Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy • Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) • Adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements • Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown • Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1PDGFRα fusion kinase negative or unknown • Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) • Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). • Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.	• Newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. • chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. • Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.	• The treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The study is ongoing and further data will be required to determine long-term outcome. • The treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib.
Risk Management	No risk management measures beyond labeling	No risk management measures beyond labeling	REMS: Medication Guide and Communication Plan
Box Warning	n/a	n/a	QT Prolongation Sudden Death). Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome Avoid concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors Avoid food 2 hours before and 1 hour after taking dose
Warning & Precautions	• *Fluid Retention and Edema* • *Hematologic Toxicity* • *Severe Congestive Heart Failure and Left Ventricular*	• *Myelosuppression* • *Bleeding Related Events (mostly associated with severe thrombocytopenia*	• *Myelosuppression* • *QT Prolongation* • *Sudden Deaths*

Established & (Trade Name)	**Imatinib (GLEEVEC)** NDA 021335; NDA 021588 (Novartis)	**Dasatinib (SPRYCEL)** NDA 021986; 022072 (BMS)	**Nilotinib (TASIGNA)** NDA 022068 (Novartis)
	Dysfunction • *Hepatotoxicity* • *Hemorrhage* • *Gastrointestinal Disorders* • *Hypereosinophilic Cardiac Toxicity* • *Dermatologic Toxicities* • *Hypothyroidism* • *Toxicities from Long-Term Use* • *Use in Pregnancy* • *Children and Adolescents* • *Tumor Lysis Syndrome* • *Driving and Using Machinery*	• *Fluid Retention* • *QT Prolongation* • *Congestive Heart Failure, Left Ventricular Dysfunction and Myocardial Infarction* • *Pulmonary Arterial Hypertension (PAH)* • *Use in Pregnancy*	• *Elevated Serum Lipase* • *Hepatotoxicity* • *Electrolyte Abnormalities* • *Drug Interactions* • *Food Effects* • *Hepatic Impairment* • *Tumor Lysis Syndrome* • *Total Gastrectomy* • *Lactose* • *Monitoring Laboratory Tests* • *Use in Pregnancy*
Pregnancy Category	D	D	D

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/s/

CYNTHIA L LACIVITA
09/18/2012

CLAUDIA B MANZO
09/19/2012
concur