CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125359Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	November 17, 2011
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
BLA #	BL STN 125359/0
Applicant Name	EUSA Pharma (USA), Inc.
Date of Submission	October 31, 2010 (received November 1, 2010)
PDUFA Goal Date	August 2, 2011
Proprietary Name / Proper Name	Erwinaze asparaginase *Erwinia chrysanthemi*
Dosage Forms / Strength	Lyophilized powder supplied in single vials/ 10,000 International Units asparaginase *Erwinia chrysanthemi* per vial
Proposed Indication	"ERWINAZE (Erwinia L-asparaginase) is indicated as a component of a multi agent chemotherapeutic regimen for the treatment of patients with: • Acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to [redacted] (b) (4) E. coli derived asparaginase • [redacted] (b) (4)
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Erik Laughner
Medical Officer Review	Patricia Dinndorf
Pharmacology Toxicology Reviews	Dubravka Kufrin Anne M. Pilaro (Supervisory Review)
OBP Reviews (CMC)	Nikolay Spiridonov; Cristina Ausín-Moreno (DS), Jacek Cieslak and Serge Beaucage (DP); Faruk Sheikh (immunogenicity)
Facilities Review	Mary Farbman (DS), Anastasia Lolas & Halavati Suvarna (DP)
Clinical Pharmacology Reviews	Jun Yang
OSI/DBGC Reviews	Michael Skelly
DDMAC	Carole Broadnax
DSI	Robert Young
CDTL Review	Suzanne Demko
OSE/DMEPA	Loretta Holmes
OBP Project Manager/Labeling Review	Kim Rains

OND=Office of New Drugs
OBP=Office of Biotechnology Products
CMC=Chemistry, Manufacturing, and Controls
OSI=Office of Scientific Investigations
DBGC=Division of Bioequivalence and GLP Compliance
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

1. Introduction

The clinical use of asparaginase *Erwinia chrysanthemi* has been limited to replacement of *E. coli* asparaginase products as a component of a multi-drug combination chemotherapy regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) and a history of clinically significant hypersensitivity to the *E. coli*-derived asparaginase products.

The efficacy data provided in this original Biologics License Application (BLA) in support of the licensure are limited to the results of a single-arm, open-label pharmacokinetic and pharmacodynamic trial (Protocol AALL07P2) that enrolled 59 patients (1 patient was not treated) with ALL conducted by the Children's Oncology Group, with a history of hypersensitivity to pegaspargase. Approval was based on demonstration of sustained asparaginase activity at or above levels resulting in depletion of plasma asparagine concentrations of 3 μM or lower, which is an accepted surrogate measure for clinical benefit (an incremental improvement event-free survival due to the addition of asparaginase to multiagent chemotherapy). Collection of targeted adverse reactions, selected based on the extensive historical clinical experience with both *Erwinia* and *E. coli* asparaginase products, was performed in Protocol AALL07P2 and in the Erwinaze Master Treatment Protocol (EMPT), a single-arm, open-label expanded access program for patients with ALL or lymphoblastic lymphoma with a history of hypersensitivity to *E. coli*-derived asparaginases (native or pegylated).

With the exception of the CMC reviewers in OBP, all review team members recommended approval of this application. The CMC reviewers noted that all issues had been satisfactorily addressed but did not make a recommendation for or against approval.

2. Background

Acute lymphoblastic leukemia
Acute lymphoblastic leukemia (ALL) is a malignancy arising in the marrow and involving the lymphoid lineage. Based on the Surveillance Epidemiology and End Results (SEER) database, an estimated 5,730 individuals will be diagnosed with and 1,420 patients will die of ALL in 2011. From 2004-2008, the median age at diagnosis for ALL was 13 years of age. Approximately 60.3% were diagnosed under age 20. In both adults and children, multi-agent chemotherapy consisting of remission induction followed by intensification is the initial line of treatment. Since the 1970's, asparaginase products have been component of such combination regimens, however its use can be limited by development of serious toxicities (pancreatitis, thrombosis) and development of anti-product antibodies resulting in allergic reactions and loss of efficacy.

Approved products in this class
There are two asparaginase products approved by the FDA: asparaginase (Elspar®), which contains the enzyme L-asparagine amidohydrolase, type EC-2, derived from *E. coli* and pegaspargase (Oncaspar®), which is native *E. coli* asparaginase covalently linked to polyethylene glycol.

Asparaginase *Erwinia chrysanthemi outside of the US*
The drug is currently marketed in multiple countries, including Canada and the United Kingdom. Because of manufacturing difficulties, asparaginase *Erwinia* chrysanthemi was removed from the worldwide market from 2003 to 2004.

3. CMC/Device

The CMC review team provided an overall acceptability recommendation of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable with modifications as requested during the review to release testing methods and procedures. Stability testing supports an expiry of 24 months from the date of manufacture when stored at 2-8 °C, where the date of drug product manufacture is defined (b) (4) (b) (4) Stability testing also supports an expiry dating period for the drug substance of (b) (4) There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude the approval of Erwinaze. Acute toxicity studies were conducted in rats and rabbits and chronic toxicology studies were conducted in rabbits, dogs, and monkeys. For the chronic toxicology studies, a single dose was explored, precluding an assessment of the dose-toxicity relationship. The findings of these studies were generally uninformative and did not predict the clinical toxicities observed in clinical studies with both this product and other marketed asparaginase products; where mortality was observed, the cause of death was not established.

Additional toxicology studies, conforming to current regulatory standards were not required given the decades-long use in human subjects and the well-characterized toxicity profile in children with ALL. Carcinogenicity and mutagenicity studies for this protein therapeutic have not been requested, as per the ICH S9 and ICH S6 guidelines. A complete battery of fertility, embryo-fetal and pre-post-natal nonclinical developmental toxicity studies, as required for this patient population by the ICH M3 guidance, will be conducted under a post-marketing requirement.

5. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval.

Pharmacokinetics
Pharmacokinetic (PK) assessment was based on enzyme activity rather than on the direct measurement of the asparaginase molecule in serum, due to methodological issues leading to an inability to develop a reliable assay for direct measurement of the protein content.

Although the clinical trial supporting efficacy, AALL07P2, specified that samples were to be obtained to characterize the PK profile of Erwinaze, these data are not described in product labeling because the data were deemed unreliable due to sample handling and analysis issued discussed in section 11 of this review. The only reliable data available in the submission were trough serum concentrations at 48 hours post-dosing or 72 hours post-dosing with archived samples that were analyzed at a second contract research laboratory. Detailed PK characterization will not be required since the selection of the dose regimen has been established during the extensive clinical use of this product under IND.

Prior to initiation of Protocol AAL07P2, FDA evaluated the assay for measurement of asparaginase activity. For the assay validation, *E. coli* asparaginase was used as the standard and serum was used as the sample matrix. Based on the unreliability of the original data provided in the application, the methodology was modified to account for the use of alternative samples (archived samples retained for immunogenicity testing); the validation protocol was submitted to the FDA on August 4, 2011. The FDA has reviewed this protocol and accepted it with the caveat that it be expanded to include robustness. The validation report included short-term stability information for both

Erwinaze and the control (*E. coli* asparaginase) in human serum, including validation of freeze-thaw stability in human serum, and assay robustness results on the effects of pH, temperature and variations in critical reagents. Dr. Yang concluded that "Based on the evaluation of the data in this validation study, it appears that the method has the required attributes to make it suitable for its intended use."

Pharmacodynamics
Although FDA originally requested that the PK and PD trial utilize asparagine depletion (PD) as the surrogate endpoint for efficacy, on July 30, 2008, FDA issued an advice/information request letter in which FDA acknowledged EUSA Pharma's submission of data justifying the inherent unreliability of asparagine assay results arising from an inability to control for *ex vivo* metabolism. FDA indicated that asparaginase activity could serve as the primary PK study endpoint which can be reliably measured in the clinical setting and is directly related to asparagine depletion. FDA also stated that EUSA Pharma would be expected to document in a future BLA submission all due diligence to collect these samples for PD data to support the review and approval of a BLA.

The trough plasma asparagine levels were to be measured prior to dose 6 for each of the first three courses at either 48- or 72-hours post-dose and on day 9 or 10 post-dose 6 during the first course. Data were provided in the BLA for 47 patients receiving a minimum of six doses of Erwinaze per treatment course in trial AALL07P2. EUSA reported that 98% (n=47) of the patients in course 1; 97% (n=31) of the patients in course 2, and 100% (n=22) of the patients in course 3 achieved the clinically desired level of trough plasma asparagine level ≤3 μM (0.396 μg/mL). As noted by Dr. Yang, accurate measurement of asparagine levels is technically challenging due to the instability of asparagine in the sample, which is subject to *ex vivo* metabolism. Based on the inspectional findings conducted at the original research laboratory and these results are deemed unreliable. The assay methodology was never fully validated to FDA's satisfaction and the analysis of asparagine levels was not conducted at the second contract laboratory.

Immunogenicity
Immunogenicity samples were collected prior to the first dose of Erwinaze in each course, on days 8 and 22 of the first course (Course 1), and on days 6 and 15 of subsequent courses in patients in trial AALL07P2. These samples have been frozen and stored pending development of appropriately validated assay methods for assessment of binding and neutralizing antibodies to Erwinaze, including IgE antibody assessments.

QT/QTc Evaluation
The QT-IRT review states that "No definitive conclusions can be made regarding QTc effects due to Erwinaze from this study since this assessment involved single post-treatment; locally read ECGs collected at 1 hour post-dose 6 with categorical analysis only. The sponsor did not report the actual numeric values for QTc but number of patients who had absolute QTc ≥500 ms and change from baseline QTc ≥60 ms were reported. Therefore it is infeasible to derive the mean QT effect or to explore concentration-QT relationships following treatment with Erwinaze. In the absence of comparator arm data, the significance of the findings in categorical analysis is unclear." Based on this conclusion, the FDA QT-IRT team recommended that no language related to the effects of Erwinaze on QTc be included in the product labeling.

Drug Interactions
No data on drug interactions were provided in the application. Given the extensive clinical experience with asparaginase *Erwinia chrysanthemi* as a component of multi-agent chemotherapy over more than three decades, as well as the known mechanism of action of this enzyme and the lack of anticipated effects on drug metabolism through P450 pathways, there are no safety concerns and FDA will not require that drug interaction studies be conducted under post-marketing requirements.

6. Clinical/Statistical-Efficacy

This application is supported by a single-arm, multi-center, open-label, safety and clinical pharmacology trial in 58 patients with ALL who were unable to continue receiving pegaspargase or asparaginase derived from *E. coli* due to allergic reactions. The major efficacy outcome was attainment of sustained serum asparaginase activity levels of 0.1 IU/mL or higher, which is known to result in depletion of asparagine to levels that predict efficacy. Among 48 patients with available samples, all patients achieved this threshold trough level of asparaginase activity.

Efficacy of Erwinaze is demonstrated by evidence of sustained asparaginase activity during treatment, at a level that is predicted to result in sufficient asparagine depletion leading to leukemia cell death. This surrogate endpoint for efficacy has been used in cooperative group clinical trials to determine the appropriate dosing regimens for this and other asparaginase products; in the U.S., the level identified as predicting clinical efficacy is a trough asparaginase activity level of ≥ 0.1 international units (IU) per mL serum. However, some investigators have suggested that a trough asparaginase activity level of ≥ 0.4 IU/mL is considered a better predictor of clinical efficacy; therefore the analysis of this data also contains an FDA-conducted exploratory analysis using this cut-point.

Proportion of Patients in AALL07P2 with Sustained Asparaginase Activity

Trough sampling time (number of patients)	**Primary Objective** Proportion with asparaginase activity ≥ 0.1 IU/mL	**FDA Exploratory Analysis** Proportion with asparaginase activity ≥ 0.4 IU/mL
48-hour trough		
Proportion (n/N)	100% (35/35)	80% (28/35)
95% CI	(90%, 100%)	(64%, 90%)
72-hour trough		
Proportion (n/N)	100% (13/13)	38% (5/13)
95% CI	(77%, 100%)	(18%, 65%)

7. Safety

The safety of Erwinaze was evaluated in two open-label, single-arm trials, AALL07P2, and the Erwinaze Master Treatment Protocol (EMTP). The size of the population was adequate to assess safety, however the uncontrolled nature of the studies, use of concomitant anti-neoplastic medications with substantial toxicities, and targeted data collection limit conclusions. This is off-set by the many decades of clinical use of this product under IND and expanded access programs, which has been sufficient to identify the most common and most serious events.

Safety was evaluated in 58 patients treated on the clinical study and in 574 patients treated on the EMTP.

The most serious adverse reactions included allergic reactions (including anaphylaxis), pancreatitis, abnormal transaminases, coagulopathies, hemorrhage, nausea, vomiting and hyperglycemia. Common adverse reactions were similar in severity and incidence to those attributable to *E. coli*-derived asparaginase.

Immunogenicity
Serum samples were obtained during the conduct of trial AALL07P2 to evaluate for anti-product antibodies. These samples have been archived until the assay methods have been validated to reliably and sensitively detect binding, IgE, and neutralizing antibodies to Erwinaze. Results of the immunogenicity assessment will be submitted under post-marketing requirements as identified in the approval letter for this application.

8. Advisory Committee Meeting

This application for asparaginase *Erwinia chrysanthemi* was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

9. Pediatrics

Because this drug product for this indication has an orphan drug designation, it is exempt from the requirement of the Pediatric Research Equity Act. However, safety and efficacy have been established in clinical trials (AALL07P2 and EMPT) where the nearly all patients enrolled were children, adolescents, or young adults.

10. Other Relevant Regulatory Issues

The (b) (4) DBGC inspection identified major deficiencies with the sample handling and assay performance of the serum asparaginase and plasma asparagine assays, which led to a conclusion that these results could not be considered reliable. However, these issues were successfully addressed by identification of additional patient samples stored in another facility that could be tested, validation of the assay methodology including some of the aspects (freeze/thaw, short- and long-term stability) which were not controlled by the initial laboratory, and identification of a new contract laboratory. There are no other unresolved relevant regulatory issues.

11. Labeling

- Proprietary name:
  Neither the Division of Medication Error and Prevention Analysis nor the Division of Oncology Products 2 identified concerns regarding the applicant's proposed proprietary name. I concur with their decision.

- Proper name:
  The proposed proper name, which is under review by USAN, was rejected by FDA. Instead FDA assigned a proper name, asparaginase *Erwinia chrysanthemi,* which distinguishes this product for other approved asparaginase products, is easily pronounceable, and non-promotional.

- Carton and immediate container labels
  All carton/container issues have been satisfactorily resolved and there are no outstanding issues.

- Patient labeling/Medication guide
  The applicant did not propose a Medication Guide but did propose Patient labeling. Given the extensive knowledge in the pediatric oncology community of the safety profile and management of serious toxicities, a medication guide is not needed to ensure safe use. Since Erwinaze is administered by healthcare professionals as an intramuscular injection under close medical supervision, Patient labeling or a Medication Guide is not needed to ensure safe use by patients or their caregivers.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
  I concur with the recommendations of Dr. Keegan and the review team and also recommend approval of this application.

- Risk Benefit Assessment
  The benefits of ERWINAZE outweigh its risks, supporting the approval of ERWINAZE for the proposed indication in the agreed-upon product labeling.

  The benefits of ERWINAZE have been established indirectly; such data indicate that event-free survival (persistent leukemia, relapse or death) is shorter in patients who do not receive a full course of asparaginase as a component of their multi-agent chemotherapy, either due to inability to receive the drug based on allergic reactions or due to drug shortages. Sustained asparaginase activity, sufficient to deplete plasma asparagine to clinically effective levels, was demonstrated with ERWINAZE in a patient population with an unmet medical need, i.e., patients who can no longer receive *E. coli*-derived asparaginase products. In contrast, the serious risks of ERWINAZE, which include allergic reactions in 10%, pancreatitis in 4%, potentially glucose intolerance in 2%, and life-threatening hemorrhage or thrombosis with long-term morbidity in less than 1% of patients are considered acceptable by the patient and medical community in light of the serious nature of the disease, similar risks with *E-coli*-derived products, and the risks of other components of the multi-agent chemotherapy regimen used for treatment of ALL.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter for Postmarketing Requirements and Commitments.

/Richard Pazdur/ November 17, 2011

Richard Pazdur, M.D. Date
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Center for Drug Evaluation and Research