CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125359Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: Serge L. Beaucage, Ph.D
Division of Therapeutic Proteins (DTP)
Office of Biotechnology Product.

Through: Amy Rosenberg, MD
Division of Therapeutic Proteins (DTP)
Office of Biotechnology Product.

BLA Number: 125359
Product: Erwinaze (asparaginase *Erwinia chrysanthemi*)
Sponsor: EUSA Pharma (USA), Inc.

Date of Review: November 16, 2011

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA 125359 for Erwinaze manufactured at the (b) (4) (b) (4). The data submitted in this application are adequate to support the conclusion that the manufacture of Erwinaze is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use.

II. APPROVAL LETTER INFORMATION

EUSA Pharma (USA), Inc. is approved to manufacture asparaginase *Erwinia chrysanthemi* drug substance at (b) (4) (b) (4) The final formulated product will be manufactured and filled at (b) (4) and labeled and packaged at (b) (4)

The product, asparaginase *Erwinia chrysanthemi* may be labeled with the proprietary name ERWINAZE and marketed in a carton of 5 vials; each single vial containing 10,000 International Units of asparaginase *Erwinia chrysanthemi.*

The dating period for asparaginase *Erwinia chrysanthemi* shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of drug product manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for the drug substance shall be (b) (4) (b) (4). Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

EUSA Pharma (USA), Inc. is not currently required to submit samples of future lots of asparaginase *Erwinia chrysanthemi* to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

The following post-marketing commitments were agreed upon with EUSA Pharma (USA) Inc. and are listed as they appear in the approval letter:

15. To review the specifications for all release and stability test methods when the manufacture of a statistically significant number of Erwinaze Drug Substance (DS) and Drug Product (DP) lots is completed. The final report of this analysis together with any revised release and stability specifications will be submitted in accordance with 21 CFR 601.12 by October 31, 2013.

16. To validate hold times for each DS process intermediate, where applicable, in order to demonstrate that the quality of Erwinaze DS is not affected. This study should include a worst case hold scenario, defined by the cumulative maximal time for each hold step along with an evaluation of the purity and potency of process

intermediates and of the resulting DS. The complete hold times validation report and supporting test results together with any revisions in the established hold times will be submitted by December 31, 2013 in accordance with 21 CFR 601.12.

17. To increase the assay sensitivity for SDS-PAGE. The revised assay together with the validation report and supporting test results will be submitted as a CBE-30 supplement by December 31, 2011.

18. To perform size exclusion chromatography (SEC) and analytical ultracentrifugation (AUC) testing in a side-by-side analysis of Erwinaze DS samples that have been subjected to stress conditions. Results of these studies together with any revisions to your control strategy will be submitted by March 31,2012 in accordance with 21 CFR 601.12.

19. To provide a revised protocol for qualification of the current and future Erwinaze reference standards as a prior approval supplement by December 31, 2011.

20. To submit an experimental plan for evaluating and if appropriate, implementing L-asparagine, as the substrate for measuring the K_m and k_{cat} of Erwinaze DS and DP. The plan will be submitted by December 31, 2011.

21. To provide an experimental plan to assess the types and amounts of smaller sub-visible particulates (b) (4) in the final drug product under real-time and stress stability conditions along with a timetable for this work. The plan and a timescale for the subsequent assessment of the impact sub-visible particles may have on the quality, clinical safety and efficacy of Erwinaze Drug Product (DP) along with a control strategy will be provided by December 31, 2011 in accordance with 21 CFR 601.12.

22. To revise the peptide mapping method used for Erwinaze DS and DP release testing in order to enable chromatographic base-line resolution of most peptide fragments while accounting for ~98% of the protein sequence. The revised assay together with the validation report will be submitted as a prior approval supplement by September 30, 2012.

IV. EXECUTIVE SUMMARY

A. Description of PRODUCT

Erwinaze is an endogenous non-recombinant L-Asparaginase (L-asparaginase amidohydrolase) purified from *Erwinia chrysanthemi*. It is a tetrameric protein consisting of four identical polypeptide chain subunits with a combined molecular weight of approximately 140 kDa. Each individual subunit has a molecular weight of approximately 35 kDa. Each vial of the drug product is filled with an (b) (4) solution of 10,000 IU of the enzyme *Erwinia* L-asparaginase (*Erwinia chrysanthemi*), 0.5 mg of sodium chloride and 5.0 mg of glucose

monohydrate in 1 mL of water for injection. Each vial is lyophilized to provide Erwinaze drug product as a white powder.

Erwinaze is supplied in clear colorless vials (type 1 neutral glass) of 3 mL nominal volume. Each vial is closed with a (b) (4) rubber stopper and capped with a 13 mm aluminum over-seal. Physiological saline (0.9%) is the diluent used for reconstitution of the drug product and is not supplied with Erwinaze.

There is an overage of (b) (4) in regard to the potency of Erwinaze incorporated into the formulation. Although the targeted dose activity is 10,000 IU/mL, the product is filled to give a final activity of (b) (4) .

Three tests methods have been used to assess the purity of Erwinaze Drug Product. These methods are: (i) reverse phase ultra performance liquid chromatography (RP-UPLC); (ii) size exclusion high performance liquid chromatography (SE-HPLC); and (iii) ion-exchange high performance liquid chromatography (IEX-HPLC). The purity of three Erwinaze profiling batches and three validation batches is in the range of 93.6% to 94.8% by RP-UPLC, 95.2% to 98.6% by SE-HPLC and 84.2% to 89.1% by IEX-HPLC. The predominant impurities are (b) (4) (b) (4) impurities, which are biologically active to a level equivalent to (b) (4) of the enzyme activity.

The sponsor requested a categorical exclusion waiver for the environmental analysis of Erwinaze according to 21 CFR 25.31. The Division recommends approval of this request given that this application involves "biologic" substances, enzymes of microbial origin, which occur naturally in the environment and have been used extensively as described in the FDA Guidance Environmental Assessment of Human Drug and Biologics Applications. Approval of this BLA will not alter significantly the concentration or distribution of the substances or their degradation products in the environment. This is appropriate based on regulations established in part 21 CFR 25.31 (c).

(b) (4)

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VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Amy S. Rosenberg, M.D Director Division of Therapeutic Proteins	for A. Rosenberg 11-16/2011
Serge L. Beaucage, Ph.D Team Leader, Laboratory of Chemistry, Division of Therapeutic Proteins	11/16/2011
Jacek Cieślak, Ph.D Primary Reviewer, Laboratory of Chemistry, Division of Therapeutic Proteins	11/16/2011
Cristina Ausín-Moreno, Ph.D Primary Reviewer, Laboratory of Chemistry,Division of Therapeutic Proteins	11/16/2011
Nikolay Spiridonov, Ph.D Primary Reviewer, Laboratory of Chemistry,Division of Therapeutic Proteins	Nikolay Spiridonov. 11.16.2011.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Bethesda, MD 20892

November 8, 2011

11/15/2011

From: Jacek Cieślak, Ph.D., CMC reviewer, DTP, OBP, CDER
Through: Serge Beaucage, Ph.D., Team Leader, DTP, OBP, CDER 11/15/2011
Barry Cherney, Ph.D., Deputy Director, DTP, OBP, CDER 11-15-2011

Subject: Proper name for *Erwinia* L-asparaginase (ERWINAZE®), BLA 125359

USAN ballot ZZ-21 refers to *Erwinia* L-asparaginase (ERWINAZE®), manufactured by EUSA Pharma (USA), Inc. under BLA 125359. This enzyme is derived from a bacterium commonly known as *Erwinia chrysanthemi*. Currently, this product is available in Europe under the name of Erwinase. *Erwinia* L-asparaginase belongs to the class of amidohydrolase enzymes, which hydrolyse the amide function of asparagine, thereby converting it into aspartic acid and ammonia.

L-Asparaginase is indicated for the treatment of acute lymphoblastic leukemia (ALL). Currently, there are two licensed asparaginase products, namely, ELSPAR® (L-asparaginase derived from *E. coli*) and ONCASPAR® (pegylated L-asparaginase derived from *E. coli*). The clinical use of *Erwinia*-derived L-asparaginase is reserved for patients who have developed hypersensitivity to the *E. coli*-derived asparaginases; its dosage recommendation is unique and not interchangeable with those of the *E. coli*-derived enzymes.

ERWINAZE is a freeze-dried white powder containing 10,000 IU of *Erwinia* L-asparaginase, 0.5 mg of sodium chloride and 5 mg of glucose monohydrate. ERWINAZE is formulated as a sterile solution after reconstitution in 1 or 2 mL sodium chloride (0.9%) for injection, and is administered by intramuscular injection.

The two ballot choices, proposed (in this order) by the USAN staff, are:

(b) (4)

(b) (4)

(b) (4)

With the objective of distinguishing Erwinia-derived asparaginase from other natural bacterial asparaginases (e.g. *Wolinella* or *E. coli* asparaginases) and from recombinant or PEGylated asparaginases, asparaginase *Erwinia chrysanthemi* is proposed as a proper name for ERWINAZE, as it identifies the class of the enzyme and its bacterial source. This name selection is consistent with previous decisions by the FDA where similar enzymes derived from different organisms include within the USAN name both the enzyme class and the genus/species the protein is derived from; an example is: "collagenase clostridium histolyticum" for XIAFLEX®.

Recommendation:

The selection of asparaginase *Erwinia chrysanthemi* as a proper name for ERWINAZE® is recommended. The selection of this name was communicated to Steven Kozlowski, Director of the Office of Biotechnology Product and he concurred with the recommendation.

MEMORANDUM

Date: October 24, 2011

To: BLA 125359 file

Nikolay Spiridonov 10.28.2011.

From: Nikolay Spiridonov, Ph.D., Quality Reviewer, DTP, OBP, OPS, CDER

Through: Serge Beaucage, Ph.D., Team Leader, DTP, OBP, OPS, CDER

Serge Beaucage 10/28/11

Subject: Review of correspondence regarding request for information BLA 125359/17: (b) (4) (b) (4) from Erwinaze Drug Substance

Product: Erwinase (Erwinia L-asparaginase)

Indication: Therapy for Acute Lymphoblastic Leukemia (ALL) or for the treatment of ALL patients with hypersensitivity to (b) (4) Asparaginase

Sponsor: EUSA Pharma (USA), Inc.

RPM: Erik Laughner

Received: August 31, 2011 (amendment 125359/17)

Addendum to Review of Erwinaze Drug Substance Manufacturing Process

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Bethesda, MD 20892

BLA STN 125359

Manufacturer
EUSA Pharma (USA), Inc.

Reviewer: Jacek Cieslak, Ph.D. 10/24/2011

TL Reviewer: Serge L. Beaucage, Ph.D. Serge Beaucage 10/24/11

Division of Therapeutic Proteins

ADDENDUM 1
October 14, 2011

Background information.
On July 12, 2011 a list of all unresolved deficiencies was send to EUSA Pharma including CMC comments. FDA received a response from EUSA Pharma on July 22, 2011 including their responses to all CMC questions and a request for the meeting. After reviewing all the responses provided by Sponsor, FDA sent the comments with request to further discussed/clarify some items. The meeting (teleconference) took place on August 5, 2011 and all the CMC deficiencies were resolved during that meeting. It was established that EUSA Pharma would submit additional material for review in 2 portions, by the end of September and October. The bulk of the additional information was submitted in the September submission. Several questions resulted in future PMC submissions, the list can be found at the end of this document. During the meeting FDA requested additional stability data, which could be used to determine Erwinaze shelf life. The update was submitted on August 31, 2011 and reviewed.

This memorandum is the review of all CMC material submitted by EUSA Pharma after July 11, 2011.

(b) (4)

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(b) (4)

[redacted]

LIST OF ALL CMC POST-MARKETING COMMITMENTS

1. New PMCs:

   a. To review the specifications for all release and stability test methods when the manufacture of a statistically significant number of Erwinaze DS and DP lots is completed. The analysis together with any revised release and stability specifications will be submitted by December 31, 2013.

b. To validate hold times for each DS process intermediate, where applicable, in order to demonstrate that the quality of Erwinaze DS is not affected. This study should include a worst case hold scenario, defined by the cumulative maximal time for each hold step along with an evaluation of the purity and potency of process intermediates and of the resulting DS. The complete hold times validation report and supporting test results will be submitted by December 31, 2013.

2. PMCs already discussed with the sponsor:

   a. To increase the assay sensitivity for SDS-PAGE. The revised assay together with the validation report and supporting test results will be submitted by December 31, 2011.

   b. To perform SEC and AUC testing in a side-by-side analysis of Erwinaze DS samples that have been subjected to stress conditions. Results of these studies will be submitted by March 31, 2012.

   c. To provide a revised protocol for qualification of the current and future Erwinaze reference standards by December 31, 2011.

   d. To submit an experimental plan for evaluating L-asparagine, as the substrate for measuring the K_m and k_{cat} of Erwinaze DS and DP, by December 31, 2011.

   e. To provide an experimental plan to assess the types and amounts of smaller sub-**visible particulates** (b) (4) in the final drug product under real-time and stress stability conditions along with a timetable for this work. The plan and also a timescale for the subsequent assessment of the impact sub-visible particles may have on the quality, clinical safety and efficacy of Erwinaze DP along with a control strategy, will be provided by December 31, 2011.

   f. To revise the peptide mapping method used for DS and DP release testing in order to enable chromatographic base-line resolution of most peptide fragments while accounting for ~98% of the protein sequence. The revised assay together with the validation report will be submitted by September 30, 2012.

Addendum 1

BLA STN 125359

Manufacturer
EUSA Pharma (USA) Inc

Reviewer: Cristina Ausín-Moreno Cristina Ausín 10/21/11
LC/TL Reviewer: Serge Beaucage Serge Beaucage 10/21/11
Division of Therapeutic Proteins

OBP CMC Review Data Sheet

1. **BLA#:** STN 125359

2. **REVIEW DATE: October 13th, 2011**

3. **PRIMARY REVIEW TEAM:**
Clinical: Patricia Dinndorf
Nonclinical: Dubravka Kufrin
Product Quality Team: Nikolay Spiridonov & Cristina Ausín-Moreno (DS), Jacek Cieslak (DP)
Immunogenicity: Faruk Sheikh
BMT or Facilities: Mary Farbman (DS), Anastasia Lolas (DP)
Clinical Pharmacology: Jun Yang
OBP Labeling: Kimberly Rains
RPM: Erik Laughner

4. **MAJOR GRMP DEADLINES**
Filing Action Letter: 12/28/2010 **(PRIORITY 6 month clock)**
- Deficiencies Identified Letter (74 day letter): 01/14/2011
- Primary Reviews Due: July 5, 2011
- Send labeling/PMC/PMR/REMS to Applicant: July 5, 2011
- Secondary Reviews Due: July 9, 2011
- CDTL Review Due: July 12, 2011
- Division Director Sign-Off: July 23, 2011
- Office Director Sign-Off: August 2, 2011
- New PDUFA Date: Tuesday, 08/02/2011

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
74-day deficiency letter (IR#1)	01-14-2011
Additional deficiencies 1 (IR#2)	02-16-2011
Additional deficiencies 2 (IR#3)	07-11-2011
Additional comments from the Agency	08-04-2011

6. **SUBMISSIONS REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125359/0001	11-01-2010	Y
STN 125359 /0008 (response to IR #1)	02-23-2011	Y
STN 125359 /0010 (response to IR #1)	03-04-2011	Y
Email response to IR #3	07-25-2011	Y
STN 125359 /0016 (meeting minutes)	08-19-2011	Y
STN 125359 /0017 (response to IR #3)	08-31-2011	Y

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

Upon review of the following sections of the submission: **3.2.S.3 CHARACTERIZATION OF DRUG SUBSTANCE; 3.2.S.4 CONTROL OF DRUG SUBSTANCE; 3.2.S.5 REFERENCE STANDARDS OR MATERIALS; 3.2.S.6 CONTAINER CLOSURE SYSTEM;** and **3.2.S.7 STABILITY**

There are no objections to the use of the DS to manufacture DP.

II. List Of Deficiencies To Be Communicated

The sponsor has addressed all the deficiencies that have been communicated to them during the review cycle regarding this part the submission. The following section of the summary contains a list of all the PMCs.

III. List Of Post-Marketing Commitments

New PMCs:

1. To review the specifications for all release and stability test methods when the manufacture of a statistically significant number of Erwinaze DS and DP lots is completed. The analysis together with any revised release and stability specifications will be submitted by October 31, 2013.

2. To validate hold times for each DS process intermediate, where applicable, in order to demonstrate that the quality of Erwinaze DS is not affected. This study should include a worst case hold scenario, defined by the cumulative maximal time for each hold step along with an evaluation of the purity and potency of process intermediates and of the resulting DS. The complete hold times validation report and supporting test results will be submitted by December 31, 2013.

PMCs already discussed with the sponsor:

3. To increase the assay sensitivity for SDS-PAGE. The revised assay together with the validation report and supporting test results will be submitted by December 31, 2011.

4. To perform SEC and AUC testing in a side-by-side analyses of Erwinaze DS samples that have been subjected to stress conditions. Results of these studies will be submitted by March 31, 2012.

5. To provide a revised protocol for qualification of the current and future Erwinaze reference standards by December 31, 2011.

6. To submit an experimental plan for evaluating L-asparagine, as the substrate for measuring the K_m and k_{cat} of Erwinaze DS and DP, by December 31, 2011.

7. To provide an experimental plan to assess the types and amounts of smaller sub-visible **particulates** (b) (4) in the final drug product under real-time and stress stability conditions along with a timetable for this work. The plan and also a timescale for the subsequent assessment of the impact sub-visible particles may have on the quality, clinical safety and efficacy of Erwinaze DP along with a control strategy, will be provided by December 31, 2011..

8. To revise the peptide mapping method used for DS and DP release testing in order to enable chromatographic base-line resolution of most peptide fragments while accounting for ~98% of the protein sequence. The revised assay and together with the validation report will be submitted by September 30, 2012.

PMCs 1, 3, 6 and 8 refer to the material included in the current review. PMC 2 refers to the sections of the BLA reviewed by Nikolay Spiridonov. PMCs 1, 4, 5 and 7 refer to the sections of the BLA reviewed by Jacek Cieslak.

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Memorandum

From: **Serge L. Beaucage, Ph. D.** Serge Beaucage 10/26/11
Division of Therapeutic Proteins (DTP)
Office of Biotechnology Product.

To: **Barry Cherney, Ph. D., Deputy Division Director** Barry Cherney 10-26-11
Division of Therapeutic Proteins (DTP)
Office of Biotechnology Product.

BLA Number: **125359**
Product: **Erwinaze (Erwinia L-asparaginase)**
Sponsor: **EUSA Pharma (USA), Inc.**

Date of Review: **October 24, 2011**

This addendum to the original BLA review refers to the information requests that were communicated to the sponsor during the period of July through September 2011.

On 7/11/2011, the following deficiencies were communicated to the sponsor:

(b) (4)

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BLA STN 125359

Manufacturer
EUSA Pharma (USA) Inc

Reviewer: Nikolay Spiridonov, Ph.D. Nikolay Spiridonov. 6.21.2011.
LC/TL Reviewer: Serge Beaucage, Ph.D. Serge Beaucage 6/21/11
Division of Therapeutic Proteins

Action date: August 2, 2011

MEMORANDUM

Date: December 14, 2010

Revised May 5, 2011

To: BLA 125359 file

From: Nikolay Spiridonov, Ph.D., Quality Reviewer, DTP, OBP, OPS, CDER

Through: Barry Cherney, Ph.D., Deputy Director, DTP, OBP, OPS, CDER

Serge Beaucage, Ph.D., Team Leader, DTP, OBP, OPS, CDER

Subject: Review of BLA 125359/01: Erwinaze Drug Substance Manufacturing Process, Manufacturing Process Validation and Evaluation, Control of Materials, Critical Steps and Intermediates. Amendments to the BLA and responses through April 7, 2011

Product: Erwinase (Erwinia L-asparaginase)

Indication: Therapy for Acute Lymphoblastic Leukemia (ALL) or for the treatment of ALL patients with hypersensitivity to (b) (4) Asparaginase

Sponsor: (b) (4)

RPM: Erik Laughner

Received: October 29, 2010 (BLA 125359/01), February 23, 2011 (CMC amendment 8), February 28, 2011 (CMC amendment 9), April 4, 2011 (CMC amendment 13), April 7, 2011 (responses to Form 483).

PDUFA Date: August 2, 2011

Recommendation

I do not recommend approval of this submission.

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BLA STN 125359

Manufacturer
EUSA Pharma (USA) Inc

Reviewer: Cristina Ausín-Moreno Cristina Ausín 6/20/11
LC/TL Reviewer: Serge Beaucage Serge Beaucage 6/20/11
Division of Therapeutic Proteins

Action date: August 2, 2011

OBP CMC Review Data Sheet

1. **BLA#:** STN 125359

2. **REVIEW DATE: May 23rd, 2011**

3. **PRIMARY REVIEW TEAM:**
Clinical: Patricia Dinndorf
Nonclinical: Dubravka Kufrin
Product Quality Team: Nikolay Spiridonov & Cristina Ausín-Moreno (DS), Jacek Cieslak (DP)
Immunogenicity: Faruk Sheikh
BMT or Facilities: Mary Farbman (DS), Anastasia Lolas (DP)
Clinical Pharmacology: Jun Yang
OBP Labeling: Kimberly Rains
RPM: Erik Laughner

4. **MAJOR GRMP DEADLINES**
Filing Action Letter: 12/28/2010 **(PRIORITY 6 month clock)**
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- Send labeling/PMC/PMR/REMS to Applicant: July 5, 2011
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- Division Director Sign-Off: July 23, 2011
- Office Director Sign-Off: August 2, 2011
- New PDUFA Date: Tuesday, 08/02/2011

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
74-day deficiency letter	01-14-2011

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125359/0001	11-01-2010	Y
STN 125359 /0008 (response to IR #1)	02-23-2011	Y
STN 125359 /0010 (response to IR #1)	03-04-2011	Y

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Erwinaze
   b. Trade Name:
   c. Non-Proprietary/USAN:

d. CAS name:
e. Common name:
f. INN Name:
g. Compendial Name:
h. OBP systematic name:
i. Other Names:

8. PHARMACOLOGICAL CATEGORY:

Active Moiety: Asparaginase
FDA Unique Ingredient Identifier Code: G4FQ3CKY5R
FDA Text Phrase : asparagine-specific enzyme
National Drug File Reference Terminology (NDF-RT) Concept: Asparagine-specific Enzyme [EPC]
Numeric Unique Identifier (NDF-RT NUI): N0000175669
NDF-RT Concept Type: EPC

9. DOSAGE FORM:

The recommended dose is 25,000 IU/m2 IM three times a week for two weeks to replace each dose of pegaspargase, or each course of asparaginase treatment.

10. STRENGTH/POTENCY:

10,000 IU/vial lyophilisate that is reconstituted in 2 mL sodium chloride (0.9%).

11. ROUTE OF ADMINISTRATION:

Intramuscular

12. REFERENCED MASTER FILES:

None

13. INSPECTIONAL ACTIVITIES

Reviewer: Nikolay Spiridonov

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS

16. PRECEDENTS

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

Upon review of the following sections of the submission: **3.2.S.3 CHARACTERIZATION OF DRUG SUBSTANCE; 3.2.S.4 CONTROL OF DRUG SUBSTANCE; 3.2.S.5 REFERENCE STANDARDS OR MATERIALS; 3.2.S.6 CONTAINER CLOSURE SYSTEM;** and **3.2.S.7 STABILITY**

There are no objections to the use of the DS to manufacture DP.

II. List Of Deficiencies To Be Communicated

- The acceptance criterion for Asparaginase activity during the stability does not include an upper limit for this test. Please revise the acceptance criterion accordingly or justify why an upper limit for this test is unnecessary.

- The assay chosen by the sponsor to determined kinetic parameters corresponding to the enzymatic activity of Erwinaze is not completely appropriate because it uses a non-physiological substrate (L-aspartic acid β -hydroxamate). Please provide data supporting the comparability of the kinetic parameters (K_m and k_{cat}) when determined using L-asparagine and L-aspartic acid β-hydroxamate (AHA) as substrates for Erwinia L-asparaginase manufactured by EUSA Pharma.

- In response to the request from the Agency to improve the acceptance criteria for identification by peptide mapping, the sponsor proposed additions and changes. The new specification does not include control on disappearance of peaks and the sponsor is proposing an acceptable change in area ratio of the selected peaks of ± 15%. The sponsor should change those two things to create an appropriate acceptance criterion.

III. List Of Post-Marketing Commitments/Requirement

The sponsor's commitments regarding this section of the BLA were proposed in the original BLA submission and refer to "reviewing the specifications once additional release and stability data become available from Erwinaze batches manufactured post-BLA submission" and "provide updated stability information in the annual reports".

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BLA STN 125359

Manufacturer
EUSA Pharma (USA), Inc.

Reviewer: Jacek Cieslak, Ph.D. 06/20/2011
TL Reviewer: Serge L. Beaucage, Ph.D. Serge Beaucage 6/20/11
Division of Therapeutic Proteins

Action date: August 2, 2011

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

- Description of the dosage form: Erwinaze is a freeze-dried white powder containing 10000 IU of enzyme *Erwinia* L-asparaginase (*Erwinia chrysanthemi*), 0.5mg of sodium chloride and 5mg of glucose monohydrate. Each vial is filled with 1 mL of solution containing all ingredients (listed in the table below) which after lyophylization form Erwinaze drug product;
- Composition of the drug product is described in the table below (table copied from the submission):

	Quantity per ml / vial	Function	Quality Standard
Active Ingredient			
Crisantaspase (Erwinia L-asparaginase)	10.000 Units (nominal)	Active ingredient	In-house
Other Ingredients			
Sodium chloride	0.5mg (b) (4)	(b) (4)	USP-NF
Glucose monohydrate	5.0 mg (b) (4)	(b) (4)	USP-NF
(b) (4)	(b) (4)	(b) (4)	(b) (4)

- Physiological saline (0.9%), a diluent used for reconstitution of the drug product is not supplied with Erwinaze;
- Erwinaze is supplied in clear colorless vials (type 1 neutral glass) of 3 mL nominal volume. The size of vial neck if 13 mm, it is closed with the same size (b) (4) stopper and it is capped with 13 mm aluminum over-seal. No reconstitution diluent is provided with the product.
- Vial contents should be reconstituted in 1-2 mL of sodium chloride (0.9%) for injection and should be administered within 15 minutes of reconstitution.
- The dose is 25,000 IU/m^2 IM three times a week for two weeks to replace each dose of pegaspargase or each course of asparaginase treatment. On average the administered dose was ~19,000 IU – almost 2 vials. Unused material is discarded.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The detailed physicochemical and biological properties of the drug substance are discussed it the drug substance section. In general, the drug substance is stored as (b) (4)

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PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: 125359 **Applicant: EUSA Pharma, Inc.** **Stamp Date: 11/01/2010**

Established/Proper Name: *Erwinia* L-asparaginase (Erwinaze) **BLA/NDA Type:**

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y Y Y Y N Y Y N N N Y Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	N	Not applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	Content available in different modules
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	N	Not applicable
❑ Executed Batch Records	N	Data available in section 3.2
❑ Method Validation Package	N	Data available in section 3.2
❑ Comparability Protocols	N	Data available in section 3.2

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	Content available in different modules
Drug Substance [3.2.S]		
❑ general info	Y	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
❑ control of materials	Y	
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	
o justification of specifications		
o stability		

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CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance		
❑ control of drug substance		
o specifications		
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation		
o batch analyses		
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	Y	
o container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container, closure depyrogenation		

CTD Module 3 Contents	Present?	If not, justification, action & status
and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	
Diluent (vials or filled syringes) [3.2P′]		
❑ description and composition of diluent	N	Not applicable, diluent not provided by EUSA Pharma. Product is lyophilized.
❑ pharmaceutical development	Y N	
o preservative effectiveness	Y N	
o container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging	Y N	
(including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y N	
o Lyophilizer sterilization validation		
o Other needed validation data (hold times)	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system		
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs	Y N	
❑ stability		
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):		
❑ other devices	N	Not applicable
❑ other marketed chemicals (e.g. part	N	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y Y N	 Not applicable
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y N	 Data available in section 3.2
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	N	No changes in manufacturing process
Data demonstrating comparability of	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	 Y N Y	Not applicable
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jacek Cieslak Product Quality Reviewer(s)		12/15/2010 Date
Serge Beaucage Branch Chief/Team Leader/Supervisor	Serge Beaucage	12/15/2010 Date
Amy Rosenberg Division Director	Amy Rosenberg for A. Rosenberg	12-15-2010 Date