DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103411/5052

Enzon, Inc.
Attention: Thomas Eckhardt, Dr. sc. nat.
Vice President, Regulatory Affairs
20 Kingsbridge Road
Piscataway, NJ 08554-3969

Dear Dr. Eckhardt:

Your request to supplement your biologics license application for Pegaspargase to expand the indication for use as a component of a multi-agent first-line chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) has been approved.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, submitted July 20, 2006). Marketing product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for ages 1 to 10 years. We are waiving the pediatric study requirement for ages 0 and for 10 to 17 years for this application.

We acknowledge your written commitments to conduct postmarketing studies as described in your correspondence of July 20, 2006, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To commit to providing complete validation data for the anti-Oncaspar ELISA assay. The validation studies will provide an assessment of the sensitivity (in mass units of antibodies), specificity, and reproducibility of the assay. The cutpoint for the assay (the value that discriminates positive samples from negative samples) will be determined by using samples from unexposed patients and validated positive controls. This cut point value will be used to determine the number and percent of patients who develop antibodies to Oncaspar during clinical trials. The assay validation will be performed with insight obtained from Mire-Sluis et al. *J. of Immunol. Methods*, 2004, 289: 1-16. The assay methods, validation protocol, and validation report will be submitted by January 31, 2007.

2. To commit to development and validation of an assay to detect the presence of neutralizing antibodies to Oncaspar. Validation studies will provide an assessment of the sensitivity (in mass units of antibodies), specificity, and reproducibility of the assay. The cutpoint for the assay (the value that discriminates positive samples from negative samples) will be determined by using samples from unexposed patients and validated positive controls. This value will be used to determine the number and percent of patients who develop neutralizing antibodies to the Oncaspar during clinical trials. The assay methods, validation protocol and validation report will be submitted by January 31, 2007.

3. To commit to testing samples from patients treated with Oncaspar for the presence of binding and neutralizing antibodies to Oncaspar using the validated assays discussed in items 1 and 2 in the following study, entitled, "A Multi-Center, Open Label, Phase 1 Study Evaluating the Safety and Tolerability of Intravenous Pegaspargase in Combination with Intravenous Gemcitabine HCl in Patients with Advanced and/or Metastatic Solid Tumors and Lymphoma". This study has been submitted to IND —— A letter authorizing FDA to cross-reference the protocol submission, and specifying the location of the submission by date of submission, volume, and page numbers within IND —— will be submitted to the BLA by August 31, 2006, patient accrual will be completed by December 31, 2007, the study will be completed by July 31, 2008, and the final study report will be submitted by December 31, 2008.

4. To commit to testing samples from patients treated with Oncaspar for the presence of binding and neutralizing antibodies to Oncaspar using the validated assays discussed in items 1and 2 in patients enrolled in a larger, phase 4 clinical trial to be conducted in patients with acute lymphoblastic leukemia. The protocol will be sponsored either by a cooperative group or an academic center and a letter authorizing FDA to cross-reference the protocol submission, and specifying the location of the submission by date of submission, volume, and page numbers within the IND, will be provided by the IND sponsor and submitted to the BLA. The final protocol will be submitted to the cooperative group or academic sponsor's IND by July 1, 2007. An interim report summarizing preliminary immunogenicity testing of patients entered on the trial as of January 1, 2009 will be submitted by July 1, 2009. Patient accrual will be completed by July 1, 2011, the study will be completed by July 1, 2014, and a study report summarizing immunogenicity information will be submitted by July 1, 2015.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103411. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103411.

Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

This information will be included in your biologics license application file.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research