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*APPLICATION NUMBER:*  
**22-016**

**APPROVABLE LETTER**

AE 12/29/05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-016

Astellas Pharma US, Inc.  
Attention: Donald L. Raineri, Pharm.D.  
Senior Director, Regulatory Affairs  
Three Parkway North  
Deerfield, IL 60015-2548

Dear Dr. Raineri:

Please refer to your new drug application (NDA) 21-697 dated January 30, 2004, received January 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan hydrochloride) Injection.

We acknowledge receipt of your submissions to NDA 21-697 dated December 10, 2004, and January 10, March 22, April 6, June 30, November 18, December 1, 21 and 23, 2005.

The June 30, 2005, submission constituted a complete response to our November 30, 2004, action letter.

We have administratively unbundled the use of Vaprisol for the treatment of hypervolemic hyponatremia in hospitalized patients into NDA 22-016. The data submitted to NDA 21-697 will be cross-referenced to NDA 22-016.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiency:

The data submitted to date reveal an imbalance in cardiac-related adverse events in patients with underlying congestive heart failure treated with conivaptan hydrochloride that may signal an unacceptable risk for conivaptan hydrochloride use for this indication. While conivaptan hydrochloride administration effectively increased serum sodium in these patients, there is concern that the benefits of correcting hyponatremia will be offset by an increased occurrence of cardiac failure events and mortality. Because the hypervolemic hyponatremia population was comprised predominantly of patients with congestive heart failure, the safety of Vaprisol for the treatment of hypervolemic hyponatremia has not been established. Additional clinical trial data addressing risk versus benefit in patients with underlying congestive heart failure are therefore needed, augmented by additional data in hypervolemic hyponatremia patients without underlying congestive heart failure.

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Metabolism and Endocrinology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed for the treatment of hypervolemic hyponatremia in hospitalized patients until you have been notified in writing that the application is approved.

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If you have any questions, call Lina AlJuburi, Pharm.D., M.S., Regulatory Project Manager,  
at (301) 796-1168.

Sincerely,

*{See appended electronic signature page}*

Robert J. Meyer, M.D.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Robert Meyer

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