CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-697

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

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) 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 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.

This new drug application provides for the use of Vaprisol (conivaptan hydrochloride) Injection for the treatment of euvolemic hyponatremia in hospitalized patients.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text, per communications on December 29, 2005.

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

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-697**." Approval of this submission by FDA is not required before the labeling is used.

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 are waiving the pediatric study requirement for ages 0 to 6 years and deferring pediatric studies for ages 6 to 18 years, inclusive, for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of euvolemic hyponatremia in hospitalized pediatric patients ages 6 to 18 years, inclusive.

   Final Report Submission: October 31, 2010

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitments.**"

We remind you of your postmarketing study commitments in your submission dated, December 23, 2005. These commitments are listed below.

2. A controlled clinical trial to determine whether a loading dose is needed for efficacy of conivaptan hydrochloride for the treatment of hyponatremia, and whether a regimen that does not include a loading dose could have a lower risk of adverse events, particularly infusion site reactions.

Protocol Submission:	June 30, 2006
Study Start:	September 29, 2006
Final Report Submission:	January 31, 2008

3. A warfarin interaction study using the full labeled dose of conivaptan hydrochloride.

Protocol Submission:	submitted on October 26, 2005
Study Start:	started in November 2005
Final Report Submission:	January 31, 2007

Submit clinical protocols to your IND for this product. Submit all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol,**" "**Postmarketing Study Commitment Final Report,**" or "**Postmarketing Study Commitment Correspondence.**"

We also acknowledge your December 23, 2005, agreement to conduct the following studies:

A. A study to establish the durability of the effect on serum sodium of conivaptan hydrochloride after completion of conivaptan therapy. This study will include daily data for at least one week following discontinuation of conivaptan.

B. A special population study of full-dose conivaptan hydrochloride in patients with underlying hepatic impairment.

C. A special population study of full-dose conivaptan hydrochloride in patients with underlying renal impairment.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolism and Endocrinology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serous adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Enclosure: Package Insert, Immediate Container Label and Carton Label