DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21697/S-003

SUPPLEMENT APPROVAL

Astellas Pharma US, Inc.
Attention: Isabel Schemainda, Ph.D.
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Schemainda:

Please refer to your Supplemental New Drug Application (sNDA) dated July 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vaprisol (conivaptan) Injection.

We also acknowledge receipt of your amendments dated November 15, 2011 and January 27, 2012.

This Prior Approval sNDA provides for the following revisions to the labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. In **DOSAGE AND ADMINISTRATION**, the following text was revised

   FROM
   Continuous infusion: 20 mg/day over 24 hours for 2 to maximum 4 days (2.1).

   TO
   Continuous infusion: 20 mg per day over 24 hours, for 2 to 4 days (2.1).

2. In **DOSAGE AND ADMINISTRATION**, the following text was added

   Hepatic impairment: Decrease the dose in patients with moderate hepatic impairment (8.6, 12.3).

3. In **WARNINGS AND PRECAUTIONS**, the following text was revised

   FROM
   Hypervolemic hyponatremia associated with heart failure: The amount of safety data is limited. VAPRISOL should be used to raise serum sodium in such patients only after consideration of other treatment options (5.1, 6.1).

TO
Hypervolemic hyponatremia associated with heart failure: Data are limited. Consider other treatment options (5.1, 6.1).

4. In **WARNINGS AND PRECAUTIONS**, the following text was deleted

   Hepatic impairment: Decrease the dose of VAPRISOL (5.5, 8.6, 12.3).

   Renal impairment: Decrease the dose of VAPRISOL. Use in patients with severe renal impairment is not recommended (5.6, 8.7, 12.3).

5. In **USE IN SPECIFIC POPULATIONS**, the following text was added

   Severe renal impairment: VAPRISOL is not recommended (8.7, 12.3).

Revised text under **RECENT MAJOR CHANGES** to remove outdated text (i.e., text greater than one year old).

FULL PRESCRIBING INFORMATION

6. In **DOSAGE AND ADMINISTRATION (2.2)**, the following text was revised

   FROM
   VAPRISOL is compatible with 5% Dextrose Injection. VAPRISOL is physically and chemically compatible with 0.9% Sodium Chloride Injection for up to 22 hours when the two solutions are co-administered via a Y-site connection at a flow rate for VAPRISOL of 4.2 mL/hour and at flow rates for 0.9% Sodium Chloride Injection of either 2.1 mL/hour or 6.3 mL/hour. **VAPRISOL should not be administered with Lactated Ringer's Injection.**

   VAPRISOL should not be combined with any other product in the same intravenous line or container.

   TO
   VAPRISOL is compatible with 5% Dextrose Injection. VAPRISOL is physically and chemically compatible with 0.9% Sodium Chloride Injection for up to 48 hours when the two solutions are co-administered via a Y-site connection at a flow rate for VAPRISOL of 4.2 mL/hour and at flow rates for 0.9% Sodium Chloride Injection of either 2.1 mL/hour or 6.3 mL/hour.

   VAPRISOL has been shown to be incompatible with both Lactated Ringer's Injection and furosemide injection when these products are mixed in the same container; therefore,

do not combine VAPRISOL with these products in the same intravenous line or container.

VAPRISOL should also not be combined with any other product in the same intravenous line or container.

7. In **DOSAGE AND ADMINISTRATION**, the following text was added

2.3 Hepatic Impairment
In patients with moderate hepatic impairment, initiate VAPRISOL with a loading dose of 10 mg over 30 minutes followed by 10 mg per day as a continuous infusion for 2 to 4 days. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated upward to 20 mg per day *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

8. In **WARNINGS AND PRECAUTIONS**, the following text was deleted

5.5 Hepatic Impairment

Up to a 2.8-fold increase in exposure after oral administration of conivaptan has been seen in patients with moderate hepatic impairment. Adjust the dose of VAPRISOL accordingly *(see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.6 Renal Impairment
In patients with renal impairment (CL_{cr} 30 - 60 mL/min or CL_{cr} 10 - 29 mL/min), increases in exposure of 1.7-fold and 1.9-fold, respectively, were observed after oral administration of conivaptan. Adjust the dose of VAPRISOL accordingly *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*. Because of the high incidence of infusion site phlebitis (which can reduce vascular access sites) and unlikely benefit, use in patients with severe renal impairment (CL_{cr}<30 mL/min) is not recommended.

9. In **USE IN SPECIFIC POPULATIONS**, the following text was revised

FROM

8.6 Use in Patients with Hepatic Impairment

Moderate hepatic impairment produces an up to 2.8-fold increase in systemic exposure after oral administration of conivaptan. In patients with hepatic impairment (Child-Pugh Class A-C), initiate VAPRISOL with a loading dose of 10 mg followed by a continuous infusion of 10 mg over 24 hours for 2 to a maximum of 4 days. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated upward to 20 mg over 24 hours *[see Warnings and Precautions (5.5) and Clinical Pharmacology 12.3]*.

8.7 Use in Patients with Renal Impairment

The effect of renal impairment on the elimination of conivaptan after intravenous administration has not been evaluated. However, following oral administration of conivaptan, the AUCs for conivaptan in patients with renal impairment (CL_{cr} 30 - 60 mL/min or CL_{cr} 10 - 29 mL/min) were 70% and 85% higher, respectively, after a single oral dose and 58% and 69% higher, respectively, with repeated oral dosing compared to patients with normal renal function. In patients with moderate renal impairment (CL_{cr} 30 - 60 mL/min), initiate VAPRISOL with a loading dose of 10 mg followed by a continuous infusion of 10 mg over 24 hours for 2 to a maximum of 4 days. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated upward to 20 mg over 24 hours. In patients with CL_{cr} > 60 mL/min, dose adjustment is not necessary. Use in patients with severe renal impairment (CL_{cr} < 30 mL/min) is not recommended *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

TO

8.6 Use in Patients with Hepatic Impairment

No clinically relevant increase in exposure was observed in subjects with mild hepatic impairment; therefore no dose adjustment of VAPRISOL is necessary. The exposure to VAPRISOL approximately doubles with moderate hepatic impairment. The impact of severe hepatic impairment on the exposure to conivaptan has not been studied *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.7 Use in Patients with Renal Impairment

No clinically relevant increase in exposure was observed in subjects with mild and moderate renal impairment (CL_{cr} 30 – 80 mL/min). No dose adjustment of VAPRISOL is necessary. Because of the high incidence of infusion site phlebitis (which can reduce vascular access sites) and unlikely benefit, use in patients with severe renal impairment (CL_{cr}<30 mL/min) is not recommended *[see Clinical Pharmacology (12.3)]*.

10. In **CLINICAL PHARMACOLOGY/Pharmacokinetics/***Special Populations*, the following text was revised

FROM

Hepatic Impairment

The effect of hepatic impairment (including ascites, cirrhosis, or portal hypertension) on the elimination of conivaptan after intravenous administration has not been systematically evaluated. However, increased systemic exposure after oral conivaptan (up to a mean 2.8-fold increase) have been seen in patients with stable cirrhosis and moderate hepatic impairment. In study subjects without hepatic function impairment, VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.6)]*.

Renal Impairment

The effect of renal impairment on the elimination of conivaptan after intravenous administration has not been evaluated. However, following administration of oral conivaptan in patients with renal impairment (CL_{cr} 30 - 60 mL/min or CL_{cr} 10 - 29

mL/min), the AUCs for conivaptan were 70% and 85% higher, respectively, compared to patients with normal renal function. In study subjects without renal impairment, VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]*.

TO

Hepatic Impairment

The systemic exposure to conivaptan is approximately doubled in subjects with moderate hepatic impairment. No clinically relevant increase in exposure was observed in subjects with mild hepatic impairment. The impact of severe hepatic impairment on the exposure to conivaptan has not been studied *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]*.

Renal Impairment

Mild and moderate renal impairment (CL_{cr} 30 – 80 mL/min) do not affect exposure to VAPRISOL to a clinically relevant extent. Use in patients with severe renal impairment (CL_{cr} < 30 mL/min) is not recommended *[see Use in Specific Populations (8.7)]*.

Revised text in **FULL PRESCRIBING INFORMATION: CONTENTS** to reflect the above revisions.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).
We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REPORTING REQUIREMENTS

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

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Prescribing Information

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

/s/

NORMAN L STOCKBRIDGE
02/01/2012