DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21697/S-002 **SUPPLEMENT APPROVAL**

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

Dear Dr. Schemainda:

Please refer to your Supplemental New Drug Application (sNDA) dated June 25, 2009, received submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vaprisol (conivaptan) Injection.

We also acknowledge receipt of your submissions dated January 29 and April 15, 2010.

This "Prior Approval" supplemental new drug application provides for compliance with the Physician's Labeling Rule (PLR) including several revisions to the content of labeling as specified below.

1. In **INDICATIONS AND USAGE**, the following text was changed

   FROM

   VAPRISOL is indicated for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients.
   Important Limitation:
   VAPRISOL is not indicated for the treatment of congestive heart failure. VAPRISOL should only be used for the treatment of hyponatremia in patients with underlying heart failure when the expected clinical benefit of raising serum sodium outweighs the increased risk of adverse events for heart failure patients. (See **PRECAUTIONS and ADVERSE REACTIONS**).

   TO

   VAPRISOL® is indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.
   Important Limitation:
   VAPRISOL has not been shown to be effective for the treatment of the signs and symptoms of heart failure and is not approved for this indication.

It has not been established that raising serum sodium with VAPRISOL provides a symptomatic benefit to patients.

2. In **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DESCRIPTION AND HOW SUPPLIED/STORAGE AND HANDLING**, information concerning the ampule was deleted because the sponsor has ceased distribution of the ampule formulation and has no intent to market the ampule formulation in the future.

3. In **DOSAGE AND ADMINISTRATION/Preparation, Compatibility, and Stability**, the following text was added:

   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.

4. In **CONTRAINDICATIONS**, **Anuric Patients** (section 4.3)**,** the following text was added:

   In patients unable to make urine, no benefit can be expected *[see Clinical Pharmacology (12.3)]*.

5. In **WARNINGS AND PRECAUTIONS**, **Hyponatremia Associated with Heart Failure** (section 5.1), the following text was changed

   FROM

   The number of heart failure patients with hypervolemic hyponatremia who have been treated with intravenous VAPRISOL is too small to establish safety in patients with underlying congestive heart failure. (See ADVERSE REACTIONS)

   TO

   The amount of safety data on the use of VAPRISOL in patients with hypervolemic hyponatremia associated with heart failure is limited. VAPRISOL should be used to raise serum sodium in such patients only after consideration of other treatment options *[see Adverse Reactions (6.1)]*.

6. In **WARNINGS AND PRECAUTIONS**, **Overly Rapid Correction of Serum Sodium** (section 5.2), the following text was changed

   FROM

   An overly rapid increase in serum sodium concentration (>12 mEq/L/24 hours) may result in serious sequelae. In controlled clinical trials of VAPRISOL, about 9% of

patients who received VAPRISOL in doses of 20-40 mg/day IV met laboratory criteria for overly rapid correction of serum sodium, but none of these patients had permanent neurologic sequelae. Although not observed in the clinical studies with VAPRISOL, osmotic demyelination syndrome has been reported following rapid correction of low serum sodium concentrations.

TO

Osmotic demyelination syndrome is a risk associated with overly rapid correction of hyponatremia (i.e., > 12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, use slower rates of correction. In controlled clinical trials of VAPRISOL, about 9% of patients who received VAPRISOL in doses of 20-40 mg/day IV had rises of serum sodium >12 mEq/L/24 hours, but none of these patients had evidence of osmotic demyelination or permanent neurologic sequelae.

7. In **WARNINGS AND PRECAUTIONS**, **Coadministration of VAPRISOL and Drugs Eliminated Primarily by CYP3A Mediated Metabolism** (section 5.3), the following text was changed

FROM

Conivaptan is a substrate of CYP3A4. Coadministration of VAPRISOL with CYP3A4 inhibitors could lead to an increase in conivaptan concentrations. The consequences of increased conivaptan concentrations are unknown. Concomitant use of VAPRISOL with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated.

Conivaptan is a potent inhibitor of CYP3A4. VAPRISOL may increase plasma concentrations of coadministered drugs that are primarily metabolized by CYP3A4. In clinical trials of oral conivaptan hydrochloride, two cases of rhabdomyolysis occurred in patients who were also receiving a CYP3A4-metabolized HMG-CoA reductase inhibitor. Concomitant use of VAPRISOL with drugs that are primarily metabolized by CYP3A4 should be closely monitored or the combination should be avoided. If a clinical decision is made to discontinue concomitant medications at recommended doses, allow an appropriate amount of time (at least 24 hours) following the end of VAPRISOL administration before resuming these medications.

TO

In clinical trials of oral conivaptan, two cases of rhabdomyolysis occurred in patients who were also receiving a CYP3A-metabolized HMG-CoA reductase inhibitor. Avoid concomitant use of VAPRISOL with drugs eliminated primarily by CYP3A-mediated metabolism. Subsequent treatment with CYP3A substrate drugs may be initiated no

sooner than 1 week after the infusion of VAPRISOL is completed *[see Drug Interactions (7.1)]*.

8. In **WARNINGS AND PRECAUTIONS**, **Coadministration of VAPRISOL and Digoxin** (section 5.4), the following text was changed

   FROM

   Coadministration of digoxin, a P-glycoprotein substrate, with oral conivaptan resulted in a reduction in clearance and increases in digoxin Cmax and AUC values. Therefore, if digoxin is administered with VAPRISOL, the clinician should be alert to the possibility of increases in digoxin levels.

   TO

   Coadministration of digoxin with oral conivaptan resulted in a 1.8- and 1.4-fold increase in digoxin C_{max} and AUC, respectively. Monitor digoxin levels *[see Drug Interactions (7.2)]*.

9. In **WARNINGS AND PRECAUTIONS**, **Hepatic Impairment** (section 5.5), the following text was changed

   FROM

   The use of VAPRISOL in patients with hepatic impairment (including ascites, cirrhosis, or portal hypertension) has not been systematically evaluated. Increased systemic exposures after oral administration of conivaptan have been seen in patients with stable cirrhosis and moderate hepatic impairment. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without hepatic function impairment. Caution should be used when administering VAPRISOL to patients with hepatic impairment.

   TO

   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)]*.

10. In **WARNINGS AND PRECAUTIONS**, **Renal Impairment** (section 5.6), the following text was changed

    FROM

    The effect of renal impairment on the elimination of conivaptan after intravenous administration has not been evaluated. However, following oral administration of

conivaptan, the AUC for conivaptan was up to 80% higher after a single oral dose and 35% higher with repeated oral dosing in patients with renal impairment (CLcr< 60 mL/min/1.73 m2) as compared to those with normal renal function. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without renal function impairment. Caution should be used when administering VAPRISOL to patients with renal impairment.

TO

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.

11. In **WARNINGS AND PRECAUTIONS**, **Infusion Site Reactions** (section 5.7), the following text was changed

FROM

Conivaptan may cause significant injection site reactions, even with proper dilution and infusion rates. (See **ADVERSE REACTIONS**) The VAPRISOL ampule must only be administered when properly prepared and diluted (see **Preparation**). VAPRISOL should be administered via large veins, and the infusion site should be rotated every 24 hours. (See **DOSAGE AND ADMINISTRATION**)

TO

Infusion site reactions are common and can include serious reactions, even with proper infusion rates *[see Adverse Reactions (6.1)]*. Administer VAPRISOL via large veins, and rotate the infusion site every 24 hours *[see Dosage and Administration (2.1)]*.

12. In **PRECAUTIONS/Congestive Heart Failure**, the following text was deleted:

The number of heart failure patients with hypervolemic hyponatremia who have been treated with intravenous VAPRISOL is too small to establish safety in this specific population.

13. In **ADVERSE REACTIONS/Congestive Heart Failure**, the following text was deleted:

VAPRISOL should only be used in patients with underlying heart failure when the expected clinical benefit of raising serum sodium outweighs the risk of adverse events.

14. In **DRUG INTERACTIONS**, **CYP3A** (section 7.1), the following text was changed

FROM

Conivaptan is a potent inhibitor of CYP3A.

TO

Conivaptan is a potent mechanism-based inhibitor of CYP3A

15. In **DRUG INTERACTIONS**, **Warfarin** (section 7.3), the following text was changed

FROM

The effect of intravenous conivaptan on warfarin pharmacokinetics or pharmacodynamics has not been evaluated. The potential drug-drug interaction of oral conivaptan with warfarin, which undergoes major metabolism by CYP2C9 and minor metabolism by CYP3A4, was investigated in a clinical study.

The effects of oral conivaptan hydrochloride 40 mg twice daily on prothrombin time was assessed in patients receiving stable oral warfarin therapy. After 10 days of oral conivaptan administration, the S- and R-warfarin concentrations were 90% and 98%, respectively, of those prior to conivaptan administration. The corresponding prothrombin time values after 10 days of oral conivaptan administration were 95% of baseline. No effect of oral conivaptan on the pharmacokinetics or pharmacodynamics of warfarin was observed.

TO

VAPRISOL (40 mg/day for 4 days) administered with a single 25 mg dose of warfarin, which undergoes major metabolism by CYP2C9 and minor metabolism by CYP3A, increased the mean S-warfarin AUC and S-warfarin C_{max} by 14% and 17%, respectively. The corresponding prothrombin time and international normalized ratio values were unchanged.

16. In **USE IN SPECIFIC POPULATIONS** and **NONCLINICAL TOXICOLOGY,** revisions were made to avoid redundant text and to clarify nonclinical information.

17. In **USE IN SPECIFIC POPULATIONS**, **Use in Patients with Hepatic Impairment** (section 8.6) was changed

FROM

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 exposures after administration of oral conivaptan (up to a mean 2.8-fold increase) have been seen in patients with stable cirrhosis and

moderate hepatic impairment. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without hepatic function impairment. Caution should be exercised when administering VAPRISOL to patients with impaired hepatic function.

TO

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]*.

18. In **USE IN SPECIFIC POPULATIONS**, **Use in Patients with Renal Impairment** (section 8.7) was changed

FROM

The effect of renal impairment on the elimination of conivaptan after intravenous administration has not been evaluated. However, following administration of oral conivaptan, the AUC for conivaptan was up to 80% higher in patients with renal impairment (CLcr<60 mL/min/1.73 m2) as compared to those with normal renal function. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without renal function impairment. Caution should be exercised when administering VAPRISOL to patients with impaired renal function.

TO

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)]*.

19. The section **DRUG ABUSE AND DEPENDENCE** was deleted since no studies characterizing the abuse and dependence potential of conivaptan have ever been conducted.

20. In **CLINICAL PHARMACOLOGY, Pharmacokinetics** (section 12.3), Table 2 entitled "Pharmacokinetic Parameters After 20 mg Loading Dose for 30 Minutes and 20 mg/day or 40 mg/day Infusion for 4 Days" was deleted.

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) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 pending "Changes Being Effected" (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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

As required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

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: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21697	SUPPL-2	ASTELLAS PHARMA US INC	VAPRISOL (CONIVAPTAN HCL)INJECTION

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

/s/

STEPHEN M GRANT
05/27/2010
For Norman Stockbridge in his absence.