DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697/S-001

Astellas Pharma US, Inc.
Attention: Donald Raineri, Pharm.D.
Three Parkway North
Deerfield, IL 60015-2537

Dear Dr. Raineri:

Please refer to your supplemental new drug application dated March 5, 2008, received March 5, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan hydrochloride) 5 mg/mL Injection.

We also refer to your submission dated October 3, 2008.

This supplemental new drug application provides for addition of a premixed formulation of Vaprisol and the following labeling changes:

1) To change the title of the package insert:

FROM

VAPRISOL®
(conivaptan hydrochloride injection)

TO

VAPRISOL® (conivaptan hydrochloride injection) Ampule
and
VAPRISOL® (conivaptan hydrochloride injection) Premixed in 5% Dextrose in INTRAVIA® Plastic Container

2) To change the text in the **DESCRIPTION** section of the labeling:

FROM

Conivaptan hydrochloride injection is supplied as a sterile liquid in an ampule.

TO

Conivaptan hydrochloride injection is supplied as a sterile liquid in an ampule and as a sterile premixed solution with dextrose in a flexible plastic container.

3) To change the text in the **DESCRIPTION** section of the labeling:

FROM

Each ampule will deliver 20 mg conivaptan hydrochloride, 1.2 g propylene glycol, 0.4 g ethanol and Water for Injection, q.s. Lactic acid is added for pH adjustment to 3.0.

TO

VAPRISOL (conivaptan hydrochloride injection) Ampule
Each ampule will deliver 20 mg conivaptan hydrochloride, 1.2 g propylene glycol, 0.4 g ethanol and Water for Injection, q.s. Lactic acid is added for pH adjustment to 3.0.

VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose
Each container contains a clear, colorless, sterile, non-pyrogenic solution of conivaptan hydrochloride in dextrose. Each 100 mL, single-use premixed INTRAVIA Container contains 20 mg of conivaptan hydrochloride and 5 g of Dextrose Hydrous, USP. Lactic Acid, USP is added for pH adjustment to pH 3.4 to 3.8. The flexible plastic container is fabricated from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain of the chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. The flexible container has a foil overwrap. Water can permeate the plastic into the overwrap, but the amount is insufficient to significantly affect the premixed solution.

4) To add the following text in the **CONTRAINDICATIONS** section of the labeling:

VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose
Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

5) To modify the following text in the **PRECAUTIONS/Injection Site Reactions** section of the labeling:

FROM

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

TO

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**)

6) To add the following text in the **DOSAGE AND ADMINISTRATION/Preparation/Compatibility and Stability** section of the labeling:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter, discoloration or cloudiness is observed, the drug solution should not be used.

7) To change the following text in the **DOSAGE AND ADMINISTRATION/Preparation/Compatibility and Stability** section of the labeling:

FROM

Caution: VAPRISOL should be diluted only with 5% Dextrose Injection.

VAPRISOL is compatible with 5% Dextrose Injection and is stable for up to 24 hours after mixing. **VAPRISOL should not be mixed or administered with Lactated Ringer's Injection or 0.9% Sodium Chloride Injection.** Compatibility with other drugs has not been studied; therefore, VAPRISOL should not be combined with any other product in the same intravenous line or bag.

TO

VAPRISOL (conivaptan hydrochloride injection) Ampule

Caution: VAPRISOL ampule should be diluted only with 5% Dextrose Injection.

The VAPRISOL ampule is compatible with 5% Dextrose Injection and is stable for up to 24 hours after mixing. **The VAPRISOL ampule should not be mixed or administered with Lactated Ringer's Injection or 0.9% Sodium Chloride Injection.** Compatibility with other drugs has not been studied; therefore, VAPRISOL should not be combined with any other product in the same intravenous line or container.

The diluted solution of VAPRISOL should be used immediately and administration completed within 24 hours of mixing.

8) To add the following text in the **DOSAGE AND ADMINISTRATION/Preparation/Compatibility and Stability** section of the labeling:

The VAPRISOL ampule is for single use only. Discard unused contents of the ampule.

9) To add the following text in the **DOSAGE AND ADMINISTRATION/Preparation/Compatibility and Stability** section of the labeling:

VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose

VAPRISOL is supplied in a single-use 100 mL flexible INTRAVIA container containing a sterile premixed dilute, ready-to-use, nonpyrogenic solution of conivaptan hydrochloride, 0.2 mg per mL (20 mg/100 mL) in 5% dextrose. **NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.**

VAPRISOL is compatible with 5% Dextrose Injection. **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.

Loading Dose

Administer 20 mg/100 mL VAPRISOL flexible plastic container over 30 minutes.

Continuous Infusion

For patients requiring 20 mg conivaptan hydrochloride injection per day, administer one 20 mg/100 mL VAPRISOL flexible plastic container over 24 hours.

For patients requiring 40 mg conivaptan hydrochloride injection per day, administer two consecutive 20 mg/100 mL VAPRISOL flexible plastic containers over 24 hours.

Since the flexible container is for single-use only, any unused portion should be discarded.

CAUTION: **Do not use plastic containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

Directions for VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose:

Do not remove container from overwrap until ready for use. The overwrap is a moisture and light barrier. The inner container maintains the sterility of the product.

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. After removing overwrap, check for minute leaks by squeezing inner container firmly. If leaks are found, discard solution as sterility may be impaired. Do not use if the solution is cloudy or a precipitate is present.

DO NOT ADD SUPPLEMENTARY MEDICATION.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

10) To add the following text in the **STORAGE** section of the labeling:

VAPRISOL (conivaptan hydrochloride injection) Ampule

11) To add the following text in the **STORAGE** section of the labeling:

VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose

VAPRISOL in INTRAVIA Plastic Containers should be stored at 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat. Protect from freezing. Protect from light until ready to use.

12) To change the following text in the **HOW SUPPLIED** section of the labeling:

FROM

VAPRISOL® (conivaptan hydrochloride injection) is supplied in 4 mL clear glass, one-point cut ampules. Each ampule contains 20 mg conivaptan hydrochloride.

10 ampules/carton (NDC 0469-1601-04)

Rx only

Marketed by:

Astellas Pharma US, Inc.

Deerfield, IL 60015-2548

Manufactured by:

Astellas Tokai Co., Ltd. Yaizu Plant

Shizuoka 425-0072, Japan

February 2007

02272007VAP

TO

VAPRISOL (conivaptan hydrochloride injection) ampule is supplied in 4 mL clear glass, one-point cut ampules. Each ampule contains 20 mg conivaptan hydrochloride.

10 ampules/carton (NDC 0469-1601-04)

VAPRISOL (conivaptan hydrochloride injection) in 100 mL INTRAVIA Plastic Containers is supplied as a single-use, premixed solution, containing 20 mg of conivaptan hydrochloride in 5% Dextrose.

10 containers/carton (NDC 0469-1602-11)

Rx only

VAPRISOL is a registered trademark of Astellas Pharma US, Inc.
INTRAVIA is a registered trademark of Baxter International Inc.

Marketed by:

Astellas Pharma US, Inc.

Deerfield, IL 60015-2548

VAPRISOL Ampule Manufactured by:

Astellas Tokai Co., Ltd.

Yaizu Plant

Shizuoka 425-0072, Japan

VAPRISOL in INTRAVIA Plastic Container Manufactured by:

Baxter Healthcare Corporation

Deerfield, IL 60015

Revision Date: October 2008

07-19-53-243

02272007VAP

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

Please 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 this division 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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-697/S-001**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the agreed-upon carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product

Applications and Related Submissions Using the eCTD Specifications (October 2005). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-697/S-001**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
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., 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: Labeling text

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

/s/

Norman Stockbridge

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