

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-697

APPROVABLE LETTER



NDA 21-697

Yamanouchi Pharma America, Inc.
Attention: Jacquelyn Hartley
Director, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Ms. Hartley:

Please refer to your January 30, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan HCl) Injection, 5 mg/mL, 4 mL per ampule.

We acknowledge receipt of your submissions dated January 30, March 17 and 31, May 14 and 28, July 1, 2, and 15, August 16, September 15, October 22, and November 19, 2004.

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 provide the following requested information.

Clinical

1. The number of subjects receiving conivaptan at the systemic exposures associated with the dose and dosing regimen proposed for marketing is inadequate for the evaluation of the safety of conivaptan. Additional clinical trial data addressing risk versus benefit are therefore needed.
2. The lowest effective dose of intravenous conivaptan in the treatment of nonhypovolemic hyponatremia has not been established nor has the optimal dosing regimen. Given the now established lower absolute bioavailability of conivaptan when given orally, data from your oral conivaptan studies provide strong evidence that intravenous doses of conivaptan lower than those studied and proposed for marketing would be effective for raising serum sodium concentration in the target population. Additionally, serious adverse events plausibly related to hypovolemia suggest that moderation of the aquaretic effect of vasopressin antagonism may render a better safety profile of conivaptan. A study or studies to identify the most appropriate intravenous dose (one that best balances efficacy and safety) are needed.

Clinical Pharmacology and Biopharmaceutics

3. The exposure-response relationship for conivaptan may vary with renal function. A systematic analysis of the relationship between pharmacodynamic response (e.g., free water clearance) and creatinine clearance is needed.
4. The need for an initial intravenous loading dose of conivaptan is not clear, given its pharmacokinetics. Submit data to justify a loading dose (e.g., data on the efficacy with and without an initial bolus dose). Include justification for the dosing used during this bolus.

Chemistry

5. Regarding the proposed drug substance specifications (section 3.2.S.4.5):

- a. The proposed criterion for [redacted] (not more than [redacted], is not justified by the release data (mean + 3 standard deviations = [redacted] or by the submitted stability studies (not more than [redacted] months). The criterion should be revised to a lower limit to reflect the observed release and stability data since the material has been shown to have and to maintain low impurity levels.

- b. [redacted]

6. Regarding the drug product stability protocols for market lots and future drug substance changes, there is not yet sufficient commercial scale manufacturing experience to justify a reduction to annual stability testing after the initial 3 production lots. Therefore, revise these protocols to use the sampling intervals proposed in the validation protocol, i.e., [redacted] months.

7. The proposed stability criterion for [redacted] in drug product is not justified in that [redacted]. Revise the release specification to not more than [redacted].

8. Investigate [redacted] used administration sets [redacted]. The drug product formulation excluding the drug substance should be used.

Administrative

9. One financial disclosure form 3454 was received. Box #1, which reads, "As the sponsor of the submitted studies, I certify," was checked. Since some of the studies were not sponsored by Yamanouchi Pharma America, Inc., the lists of investigators should be separated by sponsor of the study and resubmitted as attachments to three copies of form 3454.
 - a. One copy of the form should have the [redacted] checked and the list of investigators in studies sponsored by Yamanouchi attached to it.
 - b. One copy of the form should have the [redacted] checked ("As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant . . .) and the corresponding list of investigators attached to it.

- c. One copy of the form should have the checked ("As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators . . .) and the corresponding list of investigators attached to it.

Labeling

10. Submit full color, scale mock-ups of carton and container labeling.

11. Container labeling

a.



b.

c.

d.



12. Carton labeling



At this time, the Agency has no objections to the use of the proprietary name Vaprisol. However, the Vaprisol name and the associated labels and labeling will be re-evaluated approximately 90 days prior to the expected approval of the NDA. The re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names at that time. Further comments on the package insert and carton and container labeling will be deferred until the aforementioned approvability issues have been addressed.

When you respond to the above deficiencies, 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:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b. Present tabulations of the new safety data combined with the original NDA data.

- c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. 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.

Although not approvability issues, we request written response to the following at your earliest convenience.

Clinical and Clinical Pharmacology and Biopharmaceutics

- A. Exploration of methods for decreasing the incidence of infusion site reactions is recommended.
- B. Conivaptan exposure in patients treated with the proposed dosage regimen was not well characterized in your application. Conivaptan plasma concentrations were measured predominantly at the end of infusion in the pivotal Phase 3 study entitled *A 4-Day, Double-Blind, Placebo-Controlled Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia*. These data are inadequate to characterize the pharmacokinetics of the drug when used as proposed. Please characterize conivaptan exposure in the target population(s) if there are any on-going or planned clinical trials. Sampling every 24 hours during infusion is suggested to characterize conivaptan pharmacokinetics in target patients.
- C. Special population studies, using the full dose planned for labeling, are needed in the elderly and in patients with hepatic impairment.
- D. A warfarin interaction study is recommended, using the full dose proposed for labeling.
- E. There appears to be a higher incidence of serious renal adverse events among patients taking conivaptan than among patients taking placebo. Information provided in your application did not permit complete characterization of the etiology of these serious renal adverse events. Information is needed that will allow us to assess whether these events are related to intravascular volume depletion or whether they represent primary nephrotoxicity. For all patients experiencing a decline in renal function, provide complete clinical and laboratory

information to the extent possible, including detailed narratives, complete urinalysis information, intake and output records, documentation of follow up to resolution, etc.

- F. We request that you characterize the durability of the effect of intravenous conivaptan on aquaresis and on serum sodium concentration after cessation of therapy and thereby address expectation of benefit with regard to inter-treatment intervals in the target population. Specifically, report the number of hours or days one can expect to see maintenance of serum sodium effect after discontinuation of the proposed intravenous regimen of conivaptan.
- G. A formal analysis of conivaptan infusion of less than 4 days duration should be considered to determine if efficacy can be achieved after a shorter period of drug administration.
- H. In Study No. 087-CL-027, entitled *A 4-Day, Double-Blind, Placebo-Controlled Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia*, multiple protocol violations occurred in which subjects received prohibited CYP3A4-metabolized drugs. The fact that subjects received other CYP3A4 metabolized drugs even in a highly controlled clinical trial setting calls into question whether restriction to short-term use in hospitalized patients will be an effective means of managing the risk of CYP3A4 drug interactions in the less-controlled setting of community use. Consider proposing a risk management plan for further reducing the likelihood that patients taking conivaptan will receive other CYP3A4-metabolized drugs.

Chemistry

I. Regarding the proposed drug substance manufacturing process (section 3.2.S.2.2):

- a. [
- b.]
- c.
- d. L

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J. Regarding the proposed raw material controls for drug substance manufacture (section 3.2.S.2.3):

- a. [
- b.]

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K. [

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L. [

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M. Provide any additional drug product stability data from the primary, site-specific, or supporting studies, including compatibility studies that are available.

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 an informal meeting or telephone conference with the Division of Metabolic and Endocrine Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer
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