

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-275**

**OTHER ACTION LETTER(s)**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-275

**COMPLETE RESPONSE**

Otsuka Pharmaceutical Company, Ltd.  
Attention: Kusuma Mallikaarjun, Ph.D.  
2440 Reasearch Blvd.  
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your new drug application (NDA) dated October 22, 2007, received October 23, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Samsca (tolvaptan) 15, 30, and 60 mg Tablets. This NDA addresses your proposed indication for the treatment of euvolemic and hypervolemic hyponatremia.

We acknowledge receipt of your submissions dated November 8, 2007, and January 9, 11, 15, and 18, February 1, 22, 27, and 29, March 14, 19, 21, and 25, April 10, 17, 25, and 29, May 6 (two), 8, 21 (two), 28, and 30 (two), June 6, 10 and 30, and July 18 and 29, 2008.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

**REQUIREMENT FOR A RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS if FDA has determined that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Samsca to ensure that the benefits of the drug outweigh the risk of overly rapid correction of serum sodium leading to osmotic demyelination. Although no known cases of osmotic demyelination were observed in Samsca's development program, there is likely to be a greater risk for this complication in the postmarketing setting, where patients may have more severe hyponatremia and may be monitored less closely. Patients may be at particular risk of overly rapid rates of serum sodium correction and osmotic demyelination if they have or develop an impaired sense of thirst (including patients with xerostoma), lack access to water, or start and stop the drug on their own.

Before this NDA may be approved, you must submit a proposed REMS and a REMS Supporting Document. Attached is a suggested template for the proposed REMS that can be completed with concise information specific to Samsca (see Appendix A). If FDA approves your NDA, the proposed

REMS will be included as an attachment to the approval letter. The REMS, once approved, will create enforceable obligations.

**REMS REQUIREMENTS**

Your proposed REMS must contain the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide. Pursuant to 21 CFR Part 208, FDA has determined that Samsca poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Samsca. FDA has determined that Samsca is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR Part 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Samsca.

**Elements to Assure Safe Use:** We have determined that the following element to assure safe use is necessary to mitigate a specific risk listed in the labeling of the drug, osmotic demyelination.

b(4)

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b(4)

**Timetable for Assessments:** We have determined that your REMS must include a timetable for assessments. These shall be no less frequent than every 6 months for the first 24 months and annually thereafter once the REMS is approved.

You should specify the interval each assessment will cover and the planned date of submission to the FDA of the assessment. Assessments should be submitted within 60 days of the close of the interval.

The REMS Supporting Document should explain the rationale for each of the elements of the REMS. It should include the following sections:

1. Background Section
2. Goals Section
3. Rationale and Description of Proposed REMS Section
  - a. Additional Potential REMS Elements (Sec 505-1(e)) – Medication Guide
  - b. Element(s) to Assure Safe Use (Sec 505-1(f)(3))
  - c. Implementation System (Sec 505-1(f)(4))

- d. Timetable for Assessment of the REMS Section (505-1(d))
- e. Information Needed for Assessments

Your REMS assessments must assess the extent to which the element to assure safe use of your REMS is meeting the goals of your REMS and whether modifications to the element or goals are needed. Your assessment of the REMS should include an evaluation of:

- a. Patients' or health care providers understanding of the serious risks of Samsca
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
- d. An assessment of use data including the extent to which Samsca is being initiated in the hospital setting.

Use the following designator at the top of the first page of the proposed REMS submission in bold, capital letters:

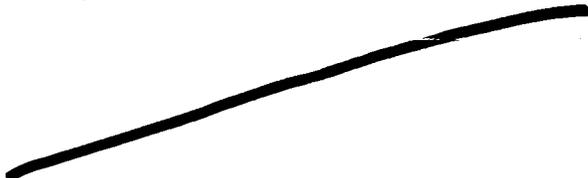
**NDA 22-275: PROPOSED REMS**

For subsequent submissions related to the proposed REMS, prominently identify the submission by including the following designator in bold, capital letters at the top of the first page of the submission:

**NDA 22-275: PROPOSED REMS-AMENDMENT**

**PROPOSED LABELING**

Proposed labeling is attached to this letter. The label has been revised to reflect the patient population



b(4)

If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

**OTHER**

If additional information relating to the safety and effectiveness of this product becomes available, revision of the labeling may be required.

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:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - 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 updated exposure information for the clinical trials (e.g. number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

Please be advised that submission of complete protocols for review and comment should be made to your IND and may be cross-referenced in your response to this letter.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

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

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

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosures: Appendix A and draft labeling text

20 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Robert Temple  
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