DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-275 **NDA APPROVAL**

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 23, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Samsca (tolvaptan) 15, 30, and 60 mg Tablets.

We acknowledge receipt of your submissions dated November 20, 2008, March 17, April 15, May 7, and May 14, 2009.

Your submission dated November 20, 2008 constituted a complete response to our August 22, 2008 action letter.

This new drug application provides for the use of Samsca (tolvaptan) for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with Syndrome of Inappropriate Antidiuretic Hormone (SIADH), heart failure and cirrhosis.

We have completed our review of this 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, 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 agreed-upon labeling text. 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 22-275**."

Submit final printed carton and container labels that are identical to the enclosed 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 22-275**." 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.

## PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Cardiovascular and Renal Products do not object to the use of the proprietary name, Samsca, for this product.

## PEDIATRIC RESEARCH EQUITY ACT (PREA)

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, or new dosing regimens are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred.

We are waiving the pediatric study requirement for ages 0 to 5 years because the necessary studies would be highly impractical because of the very low incidence of clinically significant hypervolemic and euvolemic hyponatremia in this age group.

We are deferring the requirement for submission of pediatric studies in pediatric patients aged 6-17 for this application because pediatric studies should be delayed until additional safety data have been collected. As noted in our letter dated March 13, 2009, because of the limited pre-marketing safety experience in patients with clinically significant hyponatremia, additional data are needed to provide reassurance of safety prior to initiating pediatric studies.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. A pediatric study in patients aged 6 – 17 years to obtain pharmacokinetic data pertinent to pediatric dosing of tolvaptan.

   | | |
   |---|---|
   | Final Protocol Submission: | by November 20, 2010 |
   | Study Completion Date: | by May 20, 2014 |
   | Final Report Submission: | by November 20, 2014 |

2. A study to assess the effectiveness and safety of tolvaptan in the treatment of clinically significant hypervolemic and euvolemic hyponatremia in pediatric patients aged 6 to 17.

   Final Protocol Submission: by November 20, 2010
   Study Completion Date: by May 20, 2014
   Final Report Submission: by November 20, 2014

Submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**."

## POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitment in your submission dated May 15, 2009. You commit to:

3. Submit the validation report of **(b) (4)** and consequent replacement of the dissolution test for the **(b) (4)** as a supplement to your NDA. You have also agreed to include full validation data for the **(b) (4)**

   Final Report Submission by: July 19, 2009

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol,**" "**Postmarketing Study Commitment Final Report,**" or "**Postmarketing Study Commitment Correspondence**."

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Samsca (tolvaptan) 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 the Samsca (tolvaptan) 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.

Your proposed REMS, submitted on May 14, 2009, and appended to this letter (with minor agreed-upon edits), is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following information:

a. A survey of prescribers' and patients' understanding of the risk of ODS.

b. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

c. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective action to address noncompliance.

d. Narrative summary and analysis of cases of suspected ODS reported with use of Samsca (tolvaptan).

e. Based on the information reported, an assessment of and conclusion as to whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

You have committed to submitting the final methodology and content of the patient survey at least 60 days prior to initiating the conduct of the survey.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 22-275 - REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 22-275**
**PROPOSED REMS MODIFICATION**
**REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22-275**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

## 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 www.fda.gov/cder/ddmac.

## LETTERS TO HEALTH CARE PROFESSIONALS

If you 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 an electronic copy of the letter to both this NDA and 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).

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Dan Brum, PharmD, MBA, RAC, 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

Enclosure: Labeling and REMS

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

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/s/

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Robert Temple

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