DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22275/S-005

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Company, Ltd.
Attention: Robert Ashworth, Ph.D.
Vice President, Regulatory Affairs
1 University Square Drive, Suite 500
Princeton, NJ 08540

Dear Dr. Ashworth:

Please refer to your Supplemental New Drug Application (sNDA) dated January 23, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Samsca (tolvaptan) tablets.

This Prior Approval sNDA provides for the following revisions to the labeling:

HIGHLIGHTS OF PRESCRIBING INFORMATION

Revised text under **RECENT MAJOR CHANGES** (i.e., removal of section 2.3).

FULL PRESCRIBING INFORMATION

1. In **DOSAGE AND ADMINISTRATION**, the following section was deleted

   2.3 Special Populations

   There is no need to adjust dose based on age, gender, race, cardiac or hepatic function *[see Use in Specific Populations (8) and Clinical Pharmacology (12.3)]*.

   Renal Impairment

   There is no need to adjust the dose in patients with mild to severe renal impairment (creatinine clearance 10-79 mL/min) as there is no increase in exposure to tolvaptan; tolvaptan has not been evaluated in patients with creatinine clearance < 10 mL/min or in patients undergoing dialysis. No benefit can be expected in patients who are anuric *[see Contraindications (4.5) and Clinical Pharmacology (12.3)]*.

2. In **USE IN SPECIFIC POPULATIONS**, the following text was added

There is no need to adjust dose based on age, gender, race, or cardiac function *[see Clinical Pharmacology (12.3)]*.

3. In **USE IN SPECIFIC POPULATIONS (8.7)**, the following text was revised

   FROM

   Exposure and response to tolvaptan are similar in patients with a creatinine clearance 10-79 mL/min and in patients without renal impairment. No dose adjustment is necessary. Exposure and response to tolvaptan in patients with a creatinine clearance < 10 mL/min or in patients on chronic dialysis have not been studied. No benefit can be expected in patients who are anuric *[see Contraindications (4.5)]*.

   TO

   No dose adjustment is necessary based on renal function. There are no clinical trial data in patients with CrCl < 10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients with a CrCL <10 mL/min is not recommended. No benefit can be expected in patients who are anuric *[see Contraindications (4.5)) and Clinical Pharmacology (12.3)]*.

4. In **CLINICAL PHARMACOLOGY (12.3)**, the following text was added

   In a study in patients with creatinine clearances ranging from 10-124 mL/min administered a single dose of 60 mg tolvaptan, AUC and Cmax of plasma tolvaptan were less than doubled in patients with severe renal impairment relative to the controls. The peak increase in serum sodium was 5-6 mEq/L, regardless of renal function, but the onset and offset of tolvaptan's effect on serum sodium were slower in patients with severe renal impairment *[see Use in Special Populations (8.7)]*.

Revised text in **FULL PRESCRIBING INFORMATION: CONTENTS** to reflect the above revisions.

We have completed our review of this supplemental application. 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, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. 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 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, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).
We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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

Enclosures: Prescribing Information
Medication Guide

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

/s/

NORMAN L STOCKBRIDGE
02/01/2012