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*APPLICATION NUMBER:*

**22-275**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 18, 2009  
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Subject: Review of proposed Risk Evaluation and Mitigation Strategy (REMS)  
Drug Name(s): SAMSCA™ (tolvaptan hydrochloride) Tablets  
Application Type/Number: NDA 22-275  
Applicant/Sponsor: Otsuka Pharmaceuticals, Inc.  
OSE RCM #: 2008-1857

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## 1 INTRODUCTION

This review follows a request from the Division of Cardiovascular and Renal Products (DCRP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the revised proposed Risk Evaluation and Mitigation Strategy (REMS) for Samsca (tolvaptan HCL).

## 2 BACKGROUND

Tolvaptan is a selective vasopressin antagonist with a proposed indication 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 heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

On August 22, 2008, the Agency notified the Sponsor in a Complete Response letter that a REMS consisting of a Medication Guide, communication plan, elements to assure safe use, and a timetable for submission of assessments was required for tolvaptan to ensure that the benefits of the drug outweigh the risk of overly rapid correction of sodium levels leading to osmotic demyelination. Upon review of the proposed REMS submitted October 2, 2008 and November 20, 2008, DCRP and OSE determined that although a REMS is necessary to ensure the benefit of tolvaptan outweigh its risk, it is not necessary to include elements to assure safe use as part of the REMS.

On April 8, 2009, in a REMS information Request (IR) letter, the Sponsor was informed that the key strategy for risk mitigation is hospitalization and close monitoring of serum sodium which is the standard of care for severe or symptomatic hyponatremia, the population for which tolvaptan is indicated. Thus, the proposed elements to assure safe

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~~\_\_\_\_\_~~ were not warranted for tolvaptan. The Sponsor was advised that a revised REMS proposal was required. The IR letter also included additional comments on the REMS communication materials and the information needed for assessments.

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The Sponsor submitted a revised REMS proposal on March 23, 2009 as requested. The revised REMS elements included a Medication Guide, communication plan, and a timetable for submission of assessments. DRISK reviewed the revised REMS proposal and provided additional recommendations that were communicated to the sponsor by DCRP on May 8, 2009 (Appendix A).

## 3 MATERIALS REVIEWED

- Revised proposed REMS for Samsca (NDA 22-275) dated May 13, 2009.
- DDMAC comments on REMS for Samsca (NDA 22-275) dated May 6, 2009.
- Revised proposed REMS for Samsca (NDA 22-275) dated April 15, 2009.
- Information Request letter for Samsca (NDA 22-275) dated April 8, 2009.

- OSE Review of Patient Labeling (Medication Guide) for Samsca (NDA 22-275) dated February 18, 2009.
- Proposed REMS for Samsca (NDA 22-275) dated November 20, 2008.

#### **4 PROPOSED REMS**

##### **4.1 GOALS**

The Sponsor has revised the REMS goal as indicated in the IR letter<sup>1</sup> to:

To mitigate the potential risk of osmotic demyelination syndrome (ODS) by:

- Educating healthcare providers (HCPs) on the risk of overly-rapid correction of serum sodium associated with SAMSCA and the need for initiating SAMSCA in the hospital to ensure proper titration and monitoring.
- Informing patients of the serious risk associated with the use of SAMSCA, particularly the risk of osmotic demyelination syndrome.

##### **4.2 REMS ELEMENTS**

The REMS includes a Medication Guide, communication plan, and a timetable for submission of assessments described below.

###### **4.2.1 Medication Guide**

A review of the proposed Medication Guide<sup>2</sup> was conducted and comments were provided to the Sponsor on April 8, 2009. The Sponsor accepted most changes and submitted a revised Medication Guide with some minor changes which we did not object to. Additional formatting comments were sent to the DCRP to be conveyed to the Sponsor on May 6, 2009 (Appendix B). The Sponsor has accepted all comments and has submitted a revised Medication Guide with the modified REMS proposal (dated May 13, 2009).

The Medication Guide will be dispensed with each SAMSCA prescription in accordance with 21 CFR 208.24. The Medication Guide will be included with each commercially packaged unit of use of SAMSCA. Cartons will include 10 tablets (i.e. 10 units of use) and 10 Medication Guides which equals one Medication Guide per unit of use.

###### **4.2.2 Communication Plan**

The Sponsor will implement a communication plan to healthcare providers (HCPs) in the following specialties: hospital- and community-based internal medicine specialists, cardiologists, endocrinologists, hepatologists, nephrologists, oncologists and hospital and retail pharmacists are involved in the prescribing, purchasing, dispensing or

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<sup>1</sup> Information Request letter for Samsca (NDA 22-275) dated April 8, 2009.

<sup>2</sup> OSE Review of Patient Labeling (Medication Guide) for Samsca (NDA 22-275) dated February 18, 2009.

administration of SAMSCA for both inpatient and outpatient settings a time of launch, by conveying the following information:

- The requirement to initiate and re-initiate therapy in a hospital;
- The risks associated with overly-rapid correction of serum sodium;
- Reinforcement that a patient Medication Guide should be provided to patients with every prescription of SAMSCA.

This element of the REMS is not intended to continue over the lifetime of the product; it will function only to disseminate information about the risk of ODS associated with use of SAMSCA and measures to assure safe use.

The communication plan includes a Dear Healthcare Provider Letter and a Prescriber Brochure.

#### ***4.2.2.1 Dear Healthcare Provider Letter***

The Sponsor will disseminate a Dear Healthcare Provider Letter within 60 days of the REMS approval. The purpose of the letter is to inform healthcare providers of the risk of too rapid rise of serum sodium leading to osmotic demyelination syndrome and the requirement to initiate and re-initiate SAMSCA in a hospital setting to allow for appropriate monitoring of serum sodium.

The mailing will be re-distributed every 6 months for the first year, then annually for the following 2 years.

#### ***4.2.2.2 Prescriber Brochure***

The Sponsor will provide a Prescriber Brochure to educate healthcare providers about the proper use, titration and monitoring of SAMSCA.

The Prescriber Brochure will be included with the Dear Healthcare Provider Letter, and will be distributed as indicated above. In addition, both documents will be posted on the website, [samsca.com](http://samsca.com). The brochure will also be presented and distributed by Otsuka sales representatives. This effort will be supplemented by education by Medical Science Liaisons.

#### **4.2.3 Elements to Assure Safe Use**

The REMS for Samsca does not include Elements to Assure Safe Use.

#### **4.2.4 Implementation System**

Because the REMS for Samsca does not include any Elements to Assure Safe Use, an implementation system is not required.

#### **4.2.5 Timetable for Submission of Assessments of the REMS**

The Sponsor will submit a REMS Assessment to FDA at 18 months, 3 years and 7 years following approval (see table below):

<b>Timetable for Assessment of the REMS</b>	
<b>Assessment</b>	<b>Month/Year of Submission</b>
1st REMS Assessment (18 months from approval)	November 2010
2nd REMS Assessment (3 years from approval)	May 2012
3rd REMS Assessment (7 years from approval)	May 2016

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. The Office of Compliance has reminded DCRP that the assessment is to be received by the FDA on the due date and to include this language in the REMS.

The Sponsor proposed to assess prescribers' understanding of the serious risks and safe use conditions of Samsca using surveys. We have reviewed the survey methodology and instruments and find them acceptable.

The Sponsor also proposed to assess patients' understanding of safe use and risks associated with Samsca using surveys. The sponsor proposed assessing consumer comprehension of the Medication Guide among any people rather than among patients who take Samsca. We reviewed the proposed patient survey methodology and found it to be unacceptable. Otsuka has committed to revising the methodology and questions, and submitting to FDA at least 60 days prior to conducting the survey. The submission will include, but not be limited to:

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Additionally, the sponsor has agreed to include in their assessments:

- a. a report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- b. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective action to address noncompliance
- c. Narrative summary and analysis of cases of suspected ODS reported with sue of Samsca
- d. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

Information needed for assessments (REMS Assessment Plan) is not required element of the REMS. However, this information should be included in the REMS approval letter.

## 5 CONCLUSION & RECOMMENDATIONS

We have completed our review of the proposed REMS submitted May 13, 2009, which consists of a Medication Guide, a Communication Plan, and a timetable for submission of assessments. We find the proposed REMS for Samsca to be acceptable at this time.

We recommend incorporating the following language regarding the information needed to assess the effectiveness of the REMS into the approval letter:

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

- a. A survey of prescribers' and patient's understanding of the serious risk of ODS associated with Samsca use.
- 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 sue of Samsca.
- e. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

The survey instrument and methodology for the patient survey will be submitted for FDA review at least 60 days prior to implementation. Please consult DRISK when the information is submitted.

**APPENDIX A: REMS Interim Review Comment for DCRP**

<b>Drug Name:</b> SAMSCA (Tolvaptan)	<b>BLA/NDA:</b> 22-275	<b>Date:</b> 05/08/2009
		<b>Comment Set #:</b> [2]
<b>DRISK Scientific Lead:</b>  Gita Akhavan-Toyserkani, Pharm.D., MBA. Risk Management Analyst, DRISK		<b>Reviewers:</b>  Jodi Duckhorn, MA, Patient Labeling and Education Team Leader, DRISK Brian Gordon, MA, Social Science Reviewer, DRISK Kate Heinrich, MA, Health Education Reviewer, DRISK Zarna Patel, Pharm.D., Regulatory Review Officer, DDMAC Michael Sauers, Regulatory Review Officer, DDMAC Mary Willy, Ph.D., Senior Risk Management Analyst Acting Team Leader, DRISK
<b>RCM #:</b> 2008-1857		

**Introduction:**

The comments below incorporate OSE/DDMAC's review of the proposed revised REMS for SAMSCA (tolvaptan).

**Materials Reviewed:**

- Proposed revised SAMSCA REMS submission dated April 23, 2009

**Proposed REMS Comments:**

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2. **Communication Plan:** Revise the Communication Plan as follows:

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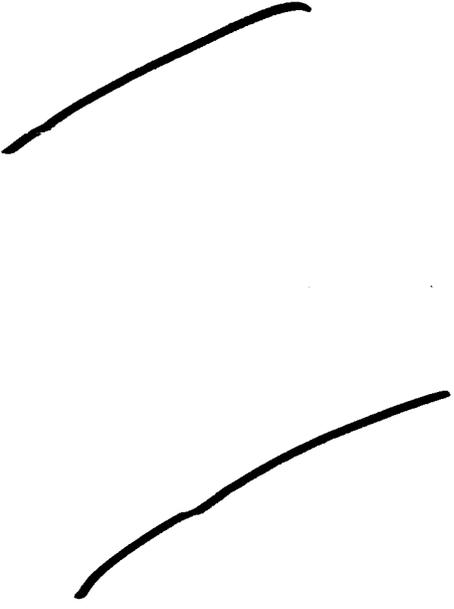
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       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)



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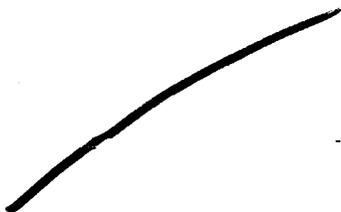
#### 4. General Comments

- Please provide a track changes and clean version of all revised materials and documents.
- Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

**APPENDIX B – Comments on Sponsor’s proposed Medication Guide revisions**

The applicant did not provide a tracked changes version of the MG in Word. The MG submitted PDF document called samsca-plr-2 -sides-20090414-layout-2.pdf was compared with the MG in the IR letter sent to the applicant on 4/8/09. We have the following comments/recommended a revision in response to the sponsor's proposed revisions:





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✓ Draft Labeling (b4)

     Draft Labeling (b5)

     Deliberative Process (b5)

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Mary Dempsey  
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DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski  
5/19/2009 07:40:46 AM  
DRUG SAFETY OFFICE REVIEWER

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Drug Evaluation I  
Division of Cardiology and Renal Products**

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**NDA/BLA #s:** NDA 22-275  
**Products:** SAMSCA (tolvaptan) 15 mg, 30 mg, and 60 mg Tablets  
**SPONSOR:** Otsuka Pharmaceutical Company, Ltd.  
**FROM:** Robert Temple, MD  
**DATE:** April 2, 2009

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The purpose of this memorandum is to document the rationale for changing the elements of the proposed REMS from the elements that were required of Otsuka in our August 22, 2008, complete response letter.

In an August 22, 2008, memorandum FDA determined that SAMSCA was required to have a REMS to mitigate the risk of osmotic demyelination, and that it should have the following elements: a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. OSE and DCRP are in agreement that the elements to assure safe use [REDACTED] that was proposed by Otsuka) are not needed at this time. **b(4)**

Although we believe a REMS is necessary to ensure the safe use of SAMSCA, upon further consideration, we do not believe that a [REDACTED] is warranted. We believe that ODS is a risk associated with any therapeutic intervention aimed at correcting serum sodium; none of the available therapies to date has indicated a need for restrictions. There is no evidence that treatment with SAMSCA places the patients at any greater risk for the development of ODS than any other treatment approach. Moreover, the most important strategy for risk mitigation is hospitalization and close monitoring of serum sodium; this is the standard of care for patients with severe or symptomatic hyponatremia, the population for which SAMSCA is indicated. In addition, we have determined that the proposed elements to assure safe use [REDACTED] that the sponsor proposed) could interfere with the availability of SAMSCA and increase the risk of interrupted therapy. Specifically, the proposed elements to assure safe use could hinder patient access to SAMSCA following hospital discharge and thereby increase the risk of clinically significant interruptions in therapy. Therefore, although we continue to believe that a REMS is necessary to ensure that the benefits of SAMSCA outweigh its risks, we have concluded that it is not necessary to include elements to assure safe use as part of the REMS. **b(4)**

The elements of the REMS will therefore be a Medication Guide, a Communication Plan, and a timetable for assessments.

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Dan Brum  
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Robert Temple  
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MEDICAL OFFICER