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*APPLICATION NUMBER:*

**22-275**

**OFFICE DIRECTOR MEMO**

# Office Director's Memo to File

**Date:** May 19, 2009

**From:** Robert Temple, MD  
Director, ODE-I

**To:** Memo to File, NDA 22-275 – Tolvaptan tablets (SAMSCA)

**Subject:** Approval of Tolvaptan f(NDA 22-275, SAMSCA) for treatment of hypervolemic and euvolemic hyponatremia. Sponsor - Otsuka

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## I. Background

A CR letter on NDA 22-275 dated 8/22/08 called for submission of a Risk Evaluation and Mitigation Strategy (REMS) directed at avoiding osmotic demyelination (a potential consequence of too-rapid correction of hyponatremia). My office director's memo of August 22, 2008 described the available data, the June 25, 2008 Cardio-Renal Advisory Committee consideration of the drug, the basis for approval, and several remaining safety considerations.

## II. Additional Information

### A. Effectiveness

The basis of approval of tolvaptan is a well-documented effect on a surrogate endpoint, a 4-5 mEq/L increase in serum sodium, shown in two 30 day studies, with results described by the primary reviewer, Dr. Aliza Thompson and in Dr. Unger's CDTL review of 8/21/08 and my review of August 25, 2008. In general, symptomatic hyponatremia patients must be treated urgently with hypertonic saline and fluid restrictions and were not in the trials. Trends toward a favorable effect on a PRO-QOL scale (SF-12) were not considered persuasive, although they trended favorably. The Ad Com plainly thought anyone with marked hyponatremia required treatment (with tolvaptan if not too severe) and needed to be prevented from going very low again, something tolvaptan could do.

## B. Labeling and REMS

Tolvaptan is indicated for 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).

Safety was well-established in a small (n=600) hyponatremia database and a large failure trial (n > 4000, with average exposure of 0.75 years) that did not show a clear benefit but supported safety.

Labeling is clear in pointing out if there is need to raise Na urgently to prevent or treat neurological symptoms, tolvaptan should not be used. It also points out that symptomatic benefit has not been established.

The Boxed warning is about too rapid correction of serum sodium, and the risk of osmotic demyelination syndrome. It also warns that SAMSCA should be initiated and re-initiated in a hospital. There is also a contraindication to use with strong CYP 450 3A inhibitors and warnings about GI bleeding in cirrhotics and the potential for dehydration and hypovolemia. Except for dry mouth/thirst; constipation, asthma, hyperglycemia, and symptoms related to urination (urgency, nocturia), there were no side effects seen in > 2% of patients.

The REMS consists of a Medication Guide and a communication plan (Dear HCP letter and Prescriber Brochure) both designed to educate providers and consumers of the need to use the drug in-hospital to avoid the osmotic demyelination syndrome and (for physicians), to avoid too-rapid Na increases. In a March 5, 2009 memo to the file we explained why some of the Elements to Assure Safe Use that were suggested in our August 22, 2008 CR action, specifically elements directed at assuring patients were hospitalized, were determined to be unnecessary. Our particular concern was that if the sponsor's proposed REMS element, which involved \_\_\_\_\_

\_\_\_\_\_ were implemented, interruption of therapy was more likely than if the drug were available in pharmacy. The requirement for Elements to Assure Safe Use (ETASU) was therefore withdrawn, leaving the REMS consisting of the Medguide and Communication Plan.

b(4)

III. Tolvaptan (SAMSCA) should be approved, as labeled, for treatment of hyponatremia.

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Robert Temple  
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MEDICAL OFFICER