Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
June 25, 2008

Location: Hilton Washington DC/Silver Spring, Maryland Ballroom,
8727 Colesville Road, Silver Spring, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the June 25, 2008 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on July 21, 2008.

I certify that I attended the June 25, 2008 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____ _____/s/_____

Elaine Ferguson M.S.,R.Ph. William R. Hiatt M.D.
Designated Federal Official Committee Chair

Meeting of the Cardiovascular and Renal Drugs Advisory Committee
25 June 2008

The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on June 25, 2008 at the Hilton Washington DC/Silver Spring, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. There were approximately one hundred and twenty (120) persons in attendance.

Issue: The committee will discuss new drug application (NDA) 22-275, tolvaptan (proposed trade name SAMSKA), Otsuka Pharmaceutical Development & Commercialization, Inc., for the proposed indication of treatment of hypervolemic and euvolemic, hyponatremia. The committee will hear presentations from the FDA and the sponsors specifically regarding change in sodium level as basis for drug approval.

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting): William R. Hiatt, M.D. (Chair), John M. Flack, M.D., M.P.H., Robert A. Harrington, M.D.,, Frederick J. Kaskel, M.D.,Ph.D., A. Michael Lincoff, MD, FACC, James D. Neaton, Ph.D. , Emil P. Paganini, M.D., F.A.C.P., F.R.C.P., Lynne L. Warner Stevenson, M.D.

Special Government Employee Consultants (Voting):
Alan G. Robinson, M.D., Sidney M.Wolfe, M.D. (Acting Consumer Representative) Paul H, Zanetti, M.D. (Patient Representative)

Industry Representative Members Present (Non-Voting):
Jonathan C Fox, MD, PhD, FACC

FDA Participants (Non-Voting):

Robert Temple, M.D., Norman Stockbridge, M.D.

Designated Federal Official:
Elaine O. Ferguson M.S.,R.Ph.

Open Public Hearing Speakers:
Richard C. Josiassen, Ph.D.

The agenda was as follows:

8:00 a.m.	Call to Order Introduction of Committee	**William Hiatt, M.D.** Chair, CRDAC
	Conflict of Interest Statement	**Elaine Ferguson, M.S.,R.Ph.** Designated Federal Official, CRDAC

8:05 a.m.	FDA Opening Remarks	**Norman Stockbridge, M.D.** Director, Cardiovascular and Renal Drug Products, CDER
	Sponsor Presentations	
8:15 a.m.	Otsuka Pharmaceutical Development & Commercialization, Inc.	
	Introduction	**Robert McQuade, PhD** Vice President, Global Medical Affairs Otsuka Pharmaceutical Development & Commercialization, Inc.
	Unmet Medical Need in Hypontremia	**Joseph Verbalis, MD** Professor of Medicine Georgetown University Medical Center
	Treatment of Hyponatremia in Heart Failure	**James Udelson, MD** Acting Chief, Division of Cardiology Tufts Medical Center Boston, MA
	Regulatory History and Overview of Clinical Development Program	**Robert McQuade, PhD** Vice President, Global Medical Affairs Otsuka Pharmaceutical Development & Commercialization, Inc.
	Tolvaptan Hyponatremia Phase 3 Program: Efficacy & Clinical Benefits	**Frank Czerwiec, MD, PhD** Senior Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc.
10:00 a.m.	**BREAK** (15 min)	
10:15 a.m.	**Sponsor Presentations continued**	
	Supportive Data from the Tolvaptan Phase III Heart Failure Program for the Treatment of Hyponatremia	**Christopher A. Zimmer, MD** Senior Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc
	Tolvaptan Safety Overview	**Joy Parris, MD**

		Senior Director, Clinical Safety and Pharmacovigilance Otsuka Pharmaceutical Development & Commercialization, Inc.
	Clinical Importance of Treating Hyponatremia	**Robert Schrier, MD** Professor of Medicine University of Colorado Health Sciences Center
	Conclusions	**Robert McQuade, PhD** Vice President, Global Medical Affairs Otsuka Pharmaceutical Development & Commercialization, Inc.
11:15 a.m.	Questions from the Committee	
12:00	**Lunch**	
1:00 p.m.	Open Public Hearing	
	FDA Presentation	
02:00 p.m.	Tolvaptan for the Treatment of Hyponatremia	**Aliza Thompson M.D**. Medical Officer, Cardiovascular and Renal Drug Products Division, CDER
02:25 p.m.	Tolvaptan for Hyponatremia FDA Overview of Patient Reported Outcomes	**Elektra Papadopoulos M.D.** Medical Officer, CDER
02:50 p.m.	**Break** (15 min)	
03:05 p.m.	Questions to the Committee	
05:00 p.m.	Adjourn	

Questions to the Committee

1) The sponsor's briefing package (pages 23-24) lists the following outcomes, signs, and symptoms of hyponatremia:

- Death
- Coma
- Seizure
- Altered consciousness
- Mental dulling
- Mental slowing
- Attention deficit
- Confusion
- Disorientation
- Agitation
- Obtundation
- Lethargy
- Lassitude
- Muscle tremor
- Muscle cramping
- Ataxia
- Gait disturbance
- Focal neurological signs
- Falls
- Forgetfulness
- Fatigue
- Dizziness
- Headache
- Nausea
- Vomiting
- Thirst
- Loss of appetite
- Taste disturbance
- Social withdrawal
- Malaise

Which of these does the Committee believe are attributable to hyponatremia, rather than to the underlying disease?

For each item you found to be attributable to hyponatremia, …

… what data show that specific therapy to correct hyponatremia produces a change in the outcome, sign, or symptom commensurate with the change in serum sodium?

… was that effect seen in the sponsor's development program?

… at what chronic serum sodium level would you expect to see the outcome, sign, or symptom manifest?

Committee response…all have the potential to be attributed to hyponatremia to more or less of a degree depending on the disease state. However these symptoms are non-specific and would be hard to distinguish among the underlying disease, hyponatremia per se and any other concomitant condition. The most serious symptoms can be attributed to acute hyponatremia.

2) The sponsor's development program demonstrated effects on serum sodium levels. Does the Committee agree that…

…these effects were seen across the different underlying diseases (SIADH, cirrhosis, heart failure)? ***Yes the committee agreed.***

…over the range of observed baseline sodium levels, tolvaptan's effect on sodium was preserved or larger at lower baseline sodium levels? ***Yes the committee agreed***

…the results were sustained during long-term (at least 30 days) use? ***Yes the committee agreed***

3) Various patient-reported outcome instruments were used in the development program for tolvaptan.

Consider the SF-12. The same battery of questions is used to derive Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Please address these scores separately in the questions below.

With regard to validity of the SF-12 PCS and MCS…

… which of the symptoms attributable to hyponatremia are assessed by the test?

… has validity been shown in a patient population like the one in the tolvaptan hyponatremia development program?

… which items of the test appear to be inappropriate or of unknown appropriateness for assessing symptoms of chronic hyponatremia?

If the SF-12 PCS or MCS have utility for measuring clinical benefit in patients with chronic hyponatremia…

… how large does the effect need to be for an individual hyponatremia patient to perceive benefit?

… are there findings of clinical benefit for tolvaptan? If so, to whom do these benefits apply?

In general, the committee was untroubled by the lack of content validity, and they agreed that the instrument was detecting something of clinical relevance. The committee also discussed the marginal statistical persuasiveness of the findings (one test out of two in one study out of two).

Consider the Hyponatremia Disease-specific Survey (HDS). The same battery of questions is used to derive Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Please address these scores separately in the questions below.

With regard to validity of the HDS PCS and MCS…

… which of the symptoms attributable to hyponatremia are assessed by the test?

… has validity been shown in a patient population like the one in the tolvaptan hyponatremia development program?

… which items of the test appear to be inappropriate or of unknown appropriateness for assessing symptoms of chronic hyponatremia?

If the HDS PCS or MCS have utility for measuring clinical benefit in patients with chronic hyponatremia…

… how large does the effect need to be for an individual hyponatremia patient to perceive benefit?

… are there findings of clinical benefit for tolvaptan? If so, to whom do these benefits apply?

Consider the Kansas City Cardiomyopathy Questionnaire.

With regard to validity of the KCCQ…

… which of the symptoms attributable to hyponatremia are assessed by the test?

… has validity been shown in a patient population like the one in the tolvaptan hyponatremia development program?

… which items of the test appear to be inappropriate or of unknown appropriateness for assessing symptoms of chronic hyponatremia?

If the KCCQ has utility for measuring clinical benefit in patients with chronic hyponatremia…

… how large does the effect need to be for an individual hyponatremia patient to perceive benefit?

… are there findings of clinical benefit for tolvaptan? If so, to whom do these benefits apply?

The committee found little evidence for clinical benefit among the HDS scores or KCCQ.

4) Are there any other benefits of treating hyponatremia—for example, on neurological or cognitive function—that have been shown in the sponsor's development program?

Most committee members agreed that the sponsor did not show them convincingly that neurological or cognitive function would improve.

5) VOTE: Is there adequate evidence that tolvaptan can be expected to produce clinical benefits in the treatment of patients with chronic hypervolemic or euvolemic hyponatremia? ***Yes = 8 No = 3***

After voting is complete, Committee members who vote yes are requested to say in whom (patient subgroup, baseline characteristics) such benefits are established.

The committee members stated that the current thought is that a low sodium is not medically good and in many patients needs to be treated. There seemed to be some agreement that a level below 130 mEq/l would need to be treated; however, the patient's symptoms, duration of hyponatremia and underlying disease state would be considered. A couple of the member stated that they would treat patients with heart failure who were hyponatremic.

6) Are there safety issues that impact approvability?

Are there findings of concern?

Bleeding, particularly in patients with cirrhosis was a concern.

Are there enough data on which to base a decision?

The lack of long term safety data was a concern.
Committee members wanted more data on the people who were excluded from the study and other specific populations. The committee made several suggestions.

7) VOTE: Should tolvaptan be approved for use in the chronic treatment of hypervolemic or euvolemic hyponatremia? ***Yes = 8 No = 3***

If you voted affirmatively, please comment on any restrictions beyond those mentioned with respect to question 5.

There was discussion among members concerning where (inpatient/outpatient) treatment should be initiated and the duration of chronic therapy.

If you voted negatively, please describe what data should be required to obtain approval.

There were several comments made with regard to how safety and clinical benefit information from this single development program may not generalize to the larger population of patients who are treated for hyponatremia, particularly treatment of patients with sodium levels below 130 who are most likely to be treated.