FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting
FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, MD
September 13, 2012

NDA 203009, lixivaptan **(Morning Session)**

DRAFT QUESTIONS

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1. **(DISCUSSION):** In the BALANCE study, a trial conducted in patients with hypervolemic hyponatremia associated with heart failure, treatment with lixivaptan resulted in a 1.2 mEq/L greater increase in serum sodium at day 7. In LIBRA and HARMONY, conducted in patients with euvolemic hyponatremia including the syndrome of inappropriate antidiuretic hormone secretion (SIADH), the treatment effect at day 7 was 2.2 and 2.4 mEq/L, respectively.

   Is lixivaptan's effect on serum sodium clinically meaningful in:

   a) patients with hypervolemic hyponatremia associated with heart failure?

   b) patients with euvolemic hyponatremia associated with SIADH?

   If not, consider lixivaptan's ability to increase free water excretion. Do you think it is possible to write instructions for use that would enable individual patients to achieve a clinically meaningful change in sodium or is a clinical study needed as a field test of the instructions for use?

2. **(DISCUSSION):** A greater number of deaths were seen in lixivaptan compared to placebo treated subjects in the BALANCE study.

   Please comment on:

   a) whether this finding raises a concern with regard to the safety of lixivaptan in patients with hypervolemic hyponatremia associated with heart failure.

   b) whether this finding raises a concern with regard to the safety of lixivaptan in patients with euvolemic hyponatremia associated with SIADH.

3. **(DISCUSSION):** The Agency has accepted changes in serum sodium as a surrogate endpoint and basis for approval of therapies for hyponatremia, but in a somewhat constrained population of patients. Both conivaptan (an intravenous V1a and V2 receptor antagonist) and tolvaptan (an oral V2 receptor antagonist) were approved based on treatment effects on serum sodium. However, the label for the oral agent specifies that the drug is indicated for the treatment of "clinically significant" hypervolemic and euvolemic hyponatremia which it goes on to define as a serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction.

Do the data from HARMONY, a trial in which lixivaptan was initiated in a monitored setting, support the safety of outpatient initiation in a population with "clinically significant" euvolemic hyponatremia?

If not, do you think a study conducted in patients with clinically significant hyponatremia testing a monitoring scheme that is likely to be feasible under real-world conditions of outpatient use could provide the necessary safety data?

4. **(VOTING):** Should lixivaptan be approved for the treatment of hypervolemic hyponatremia associated with heart failure?

   a) If you voted yes, please provide your rationale.

   b) If you voted no, please indicate what additional studies are needed to support approval.

5. **(VOTING):** Should lixivaptan be approved for the treatment of euvolemic hyponatremia associated with SIADH?

   a) If you voted yes, please provide your rationale.

   b) If you voted no, please indicate what additional studies are needed to support approval.

6. **(DISCUSSION):** If lixivaptan were approved for the treatment of hyponatremia, what should labeling say about initiation outside of a hospital setting?