

Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Tolvaptan

Product: Tolvaptan (Samsca[®])

Class of Drugs: vasopressin receptor antagonist

Reason for Use: decompensated heart failure with non-hypovolemic marked hyponatremia

Manufacturer: Otsuka Canada Pharmaceuticals Inc.

Date of Review: March 13, 2013 and September 11, 2013

CED Recommendation

The CED recommended tolvaptan (Samsca[®]) not be funded. The CED noted that tolvaptan has not been shown to improve clinical outcomes such as mortality, length of hospital stay, or rate of hospitalization. Tolvaptan is not cost-effective.

Executive Officer Decision*

Based on the CED's recommendation, the Executive Officer decided not to fund tolvaptan (Samsca[®]).

Funding Status*

Not funded through the Ontario Public Drug Programs.

* This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.

Highlights of Recommendation:

- Several clinical studies (SALT-1, SALT-2, EVEREST) demonstrated an improvement in serum sodium levels in patients with low sodium levels treated with tolvaptan compared to placebo. The studies did not show statistically significant differences in mortality or hospitalization rates between tolvaptan- and placebo-treated patients.
- Tolvaptan was fairly well tolerated by patients in the studies. Health Canada recently released a safety warning for tolvaptan in patients with polycystic kidney disease who developed serious liver injuries.
- The daily cost of tolvaptan treatment is \$250. Based on the CED's assessment of the manufacturer's economic analysis, tolvaptan is not cost-effective.
- Overall, the CED found there is evidence demonstrating that tolvaptan is effective at improving serum sodium levels. However, tolvaptan has not been shown to improve clinical outcomes such as mortality, length of hospital stay, or rate of hospitalization. Furthermore, tolvaptan is not cost-effective.

Background:

Hyponatremia (low sodium level in the blood) is the most common electrolyte disorder encountered in clinical practice. It is characterized by a serum sodium concentration $<136\text{mEq/L}$. It is generally classified as mild to moderate when the serum sodium levels are between $131 - 135\text{ mEq/L}$ or marked (severe) when the levels are $\leq 130\text{mEq/L}$. Hyponatremia can be caused by a wide range of diseases including chronic heart failure, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and liver cirrhosis. Chronic hyponatremia can be treated with dietary sodium restriction, fluid restriction, and diuretic medications.

Tolvaptan is used for the treatment of patients with decompensated heart failure with non-hypovolemic marked hyponatremia, a specific group of patients with hyponatremia.

Detailed Discussions:

- The CED reviewed tolvaptan in March 2013 and again in September 2013. The CED's reviews took into consideration:
 - Findings from the Common Drug Review and the recommendation of the Canadian Drug Expert Committee.
 - Information in the manufacturer's submissions.
- The CED evaluated two randomized, placebo-controlled trials, SALT-1 and SALT-2, in patients with moderate to severe hyponatremia, where tolvaptan was given in addition to standard therapy. Compared to placebo, tolvaptan was associated with statistically significantly greater improvements (increases) in serum sodium concentration at Day 4 and Day 30. Fifty-five percent of patients who were hyponatremic at baseline attained normalized serum sodium at day 30, compared to 25% in the placebo group. There were no statistically significant differences in mortality or hospitalization rates between the two groups.

- The CED also discussed the EVEREST trial, a randomized, double-blind, placebo-controlled trial to evaluate tolvaptan in patients hospitalized with heart failure. These patients were not necessarily hyponatremic. Tolvaptan was associated with fewer cases of death compared with placebo; however, the results did not reach statistical significance.
- The CED discussed additional post-hoc data provided by the manufacturer for the small hyponatremic subgroup of the EVEREST study. There was no significant reduction in cardiovascular (CV) death or hospitalization among those with serum sodium levels <135mEq/L treated with tolvaptan compared to placebo. There was a nominally statistically significant reduction in this outcome in patients with serum sodium levels <130mEq/L treated with tolvaptan compared to placebo (p=0.04). Furthermore, there was no difference in all-cause mortality between tolvaptan- and placebo-treated patients.
- The CED noted that alternative effective treatments for hyponatremic patients currently exist. Furthermore, sicker patients with serum sodium levels <120mEq/L were specifically excluded from the SALT trials, so the efficacy of tolvaptan in these sicker patients is unknown. Also, the ideal duration of treatment with tolvaptan is unclear.
- In the SALT and EVEREST studies, tolvaptan was fairly well tolerated. Health Canada recently released a safety warning for tolvaptan in patients with polycystic kidney disease who developed serious liver injuries.
- The CED noted there are several ongoing trials evaluating tolvaptan in the treatment of heart failure, as well as other conditions such as cirrhosis and renal disease. Therefore, additional safety data for tolvaptan is forthcoming.
- The daily cost of tolvaptan treatment is \$250. Based on the CED's assessment of the manufacturer's economic analysis, tolvaptan is not cost-effective.
- Overall, the CED found there is evidence demonstrating that tolvaptan is effective at improving serum sodium levels. However, tolvaptan has not been shown to improve clinical outcomes such as mortality, length of hospital stay, or rate of hospitalization. Furthermore, tolvaptan is not cost-effective.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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