# FINAL CDEC RECOMMENDATION

## TOLVAPTAN
## (Samsca – Otsuka Canada Pharmaceutical Inc.)
## Indication: Hyponatremia – Non-Hypovolemic and Clinically Symptomatic

**Recommendation:**
The Canadian Drug Expert Committee (CDEC) recommends that tolvaptan not be listed.

**Reasons for the Recommendation:**
1. Two placebo-controlled randomized controlled trials (RCTs) demonstrated that tolvaptan significantly improved serum sodium levels in patients with heart failure and non-hypovolemic hyponatremia; however, there was insufficient evidence that treatment with tolvaptan provides clinical benefits for mortality, morbidity, or reduced length of hospitalization relative to appropriate alternative treatments or placebo.
2. Tovalptan was not considered to be cost-effective in patients with heart failure and non-hypovolemic hyponatremia and there was insufficient pharmacoeconomic evidence to evaluate the use of tolvaptan for the treatment of non-hypovolemic hyponatremia in other patient populations.

**Background:**
Tolvaptan has a Health Canada indication for the treatment of clinically important, non-hypovolemic hyponatremia, e.g., serum sodium less than 130 mEq/L, or symptomatic hyponatremia. Tolvaptan is an oral, non-peptide, selective vasopressin V2-receptor antagonist that blocks the binding of arginine vasopressin at the V2-receptor, a receptor that mediates renal water reabsorption. It is available in 15 mg and 30 mg tablets, and it is titrated starting at 15 mg once daily and can be increased up to 60 mg once daily depending on the patient's response.

**Summary of CDEC Considerations:**
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of tolvaptan and a critique of the manufacturer's pharmacoeconomic evaluation. The manufacturer submitted a confidential price for tolvaptan.

***Patient Input Information***
No patient input was received for the tolvaptan submission.

### *Clinical Trials*

The systematic review included two RCTs of patients with mild-to-severe, non-acute hyponatremia. SALT-1 (N = 205) and SALT-2 (N = 243) were 30-day, double-blind, multicentre trials with identical protocols. Patients were randomized to either tolvaptan tablets or matching placebo. Randomization was stratified by the baseline serum sodium level (< 130 mEq/L or ≥ 130 mEq/L to < 135 mEq/L) and an underlying disease state (chronic heart failure [CHF] or non-CHF). Tolvaptan could be titrated to 30 mg or 60 mg depending on the patient's change in serum sodium level.

Enrolled patients had hyponatremia due to heart failure (33%), syndrome of inappropriate antidiuretic hormone secretion (SIADH) (25%), liver cirrhosis (27%), or unspecified (21%). The majority of the included patients (59%) were male and the mean age was 61.4 years.

### *Outcomes*

Outcomes were defined a priori in the CDR systematic review protocol. The Committee discussed the following outcomes: mortality, hospitalization, quality of life, rate of non-responders, change in plasma sodium concentration, serious adverse events, total adverse events, and withdrawals due to adverse events.

Quality of life was assessed using the physical and mental components of the SF-12 health survey. Patients were classified as non-responders if they had serum sodium levels of less than 130 mEq/L after four days of treatment.

### *Results*

### *Efficacy*

- There was no evidence of differential rates of mortality or hospitalization between tolvaptan and placebo-treated patients in either trial.
- Tolvaptan was associated with a statistically significant increase in serum sodium levels compared with the placebo group, irrespective of disease etiology (including heart failure, SIADH, and cirrhosis). The pooled mean difference (MD) was 3.71 mEq/L (95% confidence interval [CI], 3.24 to 4.2) at day 4 and 4.56 mEq/L (95% CI, 3.9 to 5.21) at day 30.
- Tolvaptan was associated with a statistically significantly lower rate of non-responders (at day 4) among patients who had a baseline serum sodium level of less than 130 mEq/L. The results were consistent in both studies and the pooled relative risk (95% CI) for non-responders at day 4 was 0.31 (0.21 to 0.45).
- Tolvaptan was associated with a statistically significant improvement in the SF-12 mental component scores compared with placebo in SALT-1, but not in SALT-2; with a 3.89 MD (95% CI, 0.59 to 7.18) in SALT-1. The difference was also statistically significant when data for both trials were pooled (MD [95% CI], 2.93 [0.71 to 5.15]). There was no statistically significant difference between tolvaptan and placebo in the SF-12 mental component scores for patients with congestive heart failure.
- The difference in the SF-12 physical component was not statistically significantly different between tolvaptan and placebo.

### *Harms (Safety and Tolerability)*

- The proportion of patients who experienced a serious adverse event was balanced between tolvaptan and placebo.

- The proportion of patients who reported an adverse event was slightly higher in the tolvaptan group (80.7%) compared with placebo (76.8%). The most commonly reported adverse events in the tolvaptan group were thirst, dry mouth, asthenia constipation, pollakiuria, and hypoglycemia.
- The proportion of patients who withdrew from the trials as a result of adverse events was similar between the tolvaptan and placebo groups.

***Cost and Cost-Effectiveness***

The manufacturer conducted a cost-utility analysis in a subgroup of patients with decompensated heart failure and marked hyponatremia (< 130 mEq/L) using data from the EVEREST trial comparing tolvaptan plus standard of care (including diuretics, digoxin, angiotensin II receptor blockers, aldosterone blockers, beta-blockers, nitrates, and/or hydralazine) with placebo plus standard of care during a two-year time horizon. The economic submission was based on a Markov model comprised of four health states: intensive care unit (ICU), normal ward, outpatient, and death. The manufacturer reported that the incremental cost-utility ratio (ICUR) for tolvaptan plus standard care is $57,936 per quality-adjusted life-year (QALY) gained when compared with placebo plus standard care.

CDR identified limitations with a number of the model assumptions used by the manufacturer:

- The manufacturer's base case assumed lower mortality with tolvaptan in the severe hyponatremia subgroup of EVEREST, but statistical significance was not demonstrated for this outcome in the clinical trials.
- The manufacturer assumed a reduced ICU stay in the tolvaptan group, but no data exist to support this.
- Length of stay in hospital and re-hospitalization (post-hoc outcomes) were associated with statistically, non-significant differences favouring tolvaptan in EVEREST.
- The maximum treatment duration was assumed to be 30 days, but the minimum duration in EVEREST was 60 days.
- Only patients with decompensated heart failure were evaluated in the economic submission. The cost-effectiveness of tolvaptan in other hyponatremic populations, specifically patients with SIADH or cirrhosis, is unknown.

Using a more conservative base case that assumes identical mortality and ICU stay for tolvaptan plus standard care compared with standard care alone, CDR noted that the ICUR increases to $271,729 per QALY gained. If other parameters that are not statistically significant (e.g., length of stay in hospital and rehospitalisation) are set to unity, the ICUR escalates to > $500,000 (as per the CDR analyses).

The daily cost of tolvaptan (30 mg to 60 mg daily) is *[confidential price removed at manufacturer's request]*). The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

**Other Discussion Points:**

The Committee noted the following:

- The manufacturer requested that tolvaptan be listed only for decompensated heart failure patients with non-hypovolemic marked hyponatremia; i.e., with serum sodium levels less than 130 mmol/L, or who are symptomatic.
- There was no evidence from SALT-1 or SALT-2 to suggest that tolvaptan reduces mortality, morbidity, length of hospitalization, or the need for ultrafiltration.
- The cost-effectiveness of tolvaptan in other hyponatremic populations other than decompensated heart failure patients is unknown.
- Tolvaptan demonstrated a statistically significant improvement in SF-12 mental component scores relative to placebo; however, the clinical relevance of this result is uncertain as the minimal clinically important difference of this outcome is unknown for patients with hypovolemic hyponatremia.

**CDEC Members:**
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

**January 16, 2013 Meeting**

**Regrets:**
None

**Conflicts of Interest:**
None

**About this Document:**
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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