**Health Canada Endorsed Important Safety Information on SAMSCA® (tolvaptan)**

February 27, 2013

**Dear Health Care Professional,**

**Subject: SAMSCA® (tolvaptan) - New warning regarding a potential risk of liver injury.**

Otsuka Canada Pharmaceutical Inc. (Otsuka) in consultation with Health Canada would like to inform you of a risk of liver injury associated with the use of SAMSCA® (tolvaptan).

SAMSCA® (15-60 mg) is indicated for the treatment of clinically important, non-hypovolemic hyponatremia (e.g., serum sodium < 130 mEq/L, or symptomatic hyponatraemia).

- SAMSCA® (tolvaptan) has the potential to cause irreversible and potentially fatal liver injury. During a large clinical trial (TEMPO 3:4)[1] in about 1400 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD), three patients out of the 958 treated with tolvaptan (60-120 mg daily), developed serious liver injuries (ALT > 3x ULN with concomitant Total Bilirubin > 2X ULN). All three patients improved following discontinuation of treatment. **SAMSCA® is not approved for the treatment of ADPKD.**

- If a patient reports symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice, liver tests should be performed promptly. SAMSCA® should be immediately discontinued and appropriate treatment initiated. Investigations should be performed to determine the cause. SAMSCA® should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with SAMSCA®.

- The ability to recover from liver injury may be impaired in patients with hyponatremia in the setting of underlying liver disease, including cirrhosis. Limiting the duration of SAMSCA® therapy may reduce the risk of developing liver injury.

During the TEMPO 3:4 trial[1] (a double-blind, 3-year, placebo-controlled trial in ADPKD patients and its open-label extension), tolvaptan was associated with an increased incidence of significant elevations of ALT (>3x ULN) compared to placebo. Specifically, 4.4% (42/958) of ADPKD patients on tolvaptan and 1.0% (5/484) of patients on placebo

exhibited elevations of ALT greater than 3x ULN. Most of the liver enzyme abnormalities were observed during the first 18 months of therapy. The elevations gradually improved after discontinuation of tolvaptan. In this trial, the maximum daily dose of tolvaptan administered (90 mg in the morning and 30 mg in the afternoon) was higher than the maximum 60 mg daily dose approved for the treatment of hyponatremia.

In other clinical trials of SAMSCA®, including the trials supporting the approved indication, liver damage has not been reported[2,3] . **However, these data are not adequate to exclude the possibility that these patients are at an increased risk for irreversible and potentially fatal liver injury.** Limiting the duration of SAMSCA® therapy may reduce the risk of developing liver injury.

The Canadian Product Monograph is currently being updated to reflect on this new safety information regarding the use of SAMSCA®.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious hepatic injury or other serious or unexpected adverse reactions in patients receiving SAMSCA® (tolvaptan) should be reported to Otsuka Canada Pharmaceutical Inc. or Health Canada at the following addresses:

Otsuka Canada Pharmaceutical Inc.
2250 Alfred Nobel Blvd.
Saint –Laurent, Quebec
H4S 2C9

Phone : 1-877-341-9245
Fax: 1-905-689-1465

**To correct your mailing address or fax number, contact Otsuka Canada Pharmaceutical Inc.**

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

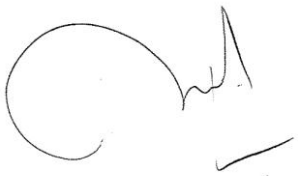
- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax

For other health product inquiries related to this communication, contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

If you have any questions or need additional information about SAMSCA®, please contact Otsuka Medical Information at 1-877-341-9245

Otsuka is committed to the highest ethical and safety standards and continues to monitor liver safety in all tolvaptan clinical trials and in post marketing reports.

Sincerely,



***Original signed by***

Otsuka Canada Pharmaceutical Inc.
per:
Khalid Mezzi, MD
Director, Medical Affairs

***References:***


1. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; the TEMPO 3:4 Trial Investigators. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2012 Nov 3. [Epub ahead of print.]

2. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C; SALT Investigators. Tolvaptan, a selective oral vasopressin V2- receptor antagonist, for hyponatremia. N Engl J Med. 2006 Nov 16;355(20):2099-112. Epub 2006 Nov 14.

3. Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS; SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol. 2010 Apr;21(4):705-12. Epub 2010 Feb 25.