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January 22, 2013

IMPORTANT DRUG WARNING

Potential Risk of Liver Injury with Use of SAMSCA® (tolvaptan)

Dear Healthcare Provider,

Otsuka would like to inform you of significant liver injury associated with the use of SAMSCA (tolvaptan).

In a large double-blind, 3-year, placebo-controlled trial (TEMPO 3:4)[1] in about 1400 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) and its open-label extension trial in patients, 3 patients treated with SAMSCA (tolvaptan) developed significant (>3x ULN) increases in serum alanine aminotransferase (ALT) with concomitant, clinically significant (>2x ULN) increases in serum total bilirubin. Following discontinuation of treatment, all 3 patients improved. An external panel of liver experts assessed these 3 cases as being either probably or highly likely to be caused by tolvaptan. These findings indicate that SAMSCA (tolvaptan) has the potential to cause irreversible and potentially fatal liver injury.

Additionally, SAMSCA (tolvaptan) was associated with an increased incidence compared to placebo of significant (greater than 3x ULN) elevations of ALT. Specifically, 4.4% (42/958) of ADPKD patients on SAMSCA (tolvaptan) and 1.0% (5/484) of patients on placebo exhibited elevations greater than 3x ULN of ALT. Most of the liver enzyme abnormalities were observed during the first 18 months of therapy. The elevations gradually improved after discontinuation of tolvaptan. In the ADPKD trials the maximum daily dose of SAMSCA 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.
SAMSCA is not approved for the treatment of ADPKD.

In other clinical trials of SAMSCA, including the trials supporting the approved indication (clinically significant euvolemic or hypervolemic hyponatremia), liver damage has not been reported.[2,3]

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However, **these data are not adequate to exclude the possibility that patients receiving SAMSCA for its indicated use of clinically significant hypervolemic and euvolemic hyponatremia are at a potential increased risk for irreversible and potentially fatal liver injury.**

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.

Healthcare providers should perform liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If hepatic injury is suspected, SAMSCA should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable 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.

Otsuka is in communication with the FDA and this issue will be closely reviewed and monitored.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING and Medication Guide.

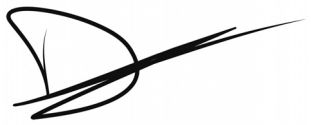
Further Information

Healthcare providers should report cases of hepatic injury or any serious adverse event to Otsuka by calling (800) 438-9927. Alternatively, report this information to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), or https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm. Reports of serious adverse events can also be mailed using the MedWatch form FDA 3500 to the Medical Products Reporting Program, 5600 Fishers Lane, Rockville, Maryland 20852-9787.

If you need additional information about SAMSCA, please contact Otsuka Medical Affairs toll-free at 1-800-441-6763 (9 AM to 5 PM ET, Monday through Friday), or visit **www.Samsca.com**.

Otsuka is committed to the highest ethical and safety standards and continues to monitor liver safety in all tolvaptan clinical trials and in postmarketing reports.[4]
The FDA reviewed and approved this letter prior to its distribution.

Sincerely,



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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.

4. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf. July 2009.