U.S. Food and Drug Administration
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Drug Safety Communications

FDA Drug Safety Communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death

Safety Announcement

[04-30-2013] The U.S. Food and Drug Administration (FDA) has determined that the drug Samsca (tolvaptan) should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially requiring liver transplant or death. Samsca is used to treat low sodium levels in the blood. An increased risk of liver injury was observed in recent large clinical trials evaluating Samsca for a new use in patients with autosomal dominant polycystic kidney disease (ADPKD) [1] (See Data Summary). FDA has worked with the manufacturer to revise the Samsca drug label to include these new limitations.

The Samsca drug label has been updated to include the following information:

- Limitation of the duration of Samsca treatment to 30 days. (*Dosage and Administration* and *Warnings and Precautions* sections)
- Removal of the indication for use in patients with cirrhosis, a condition that involves scarring of the liver due to injury or long-term disease. Use of Samsca in patients with underlying liver disease, including cirrhosis, should be avoided because the ability to recover from liver injury may be impaired. (*Indications and Usage* and *Use in Specific Populations* sections)
- Description of liver injuries seen in clinical trials of patients with autosomal dominant polycystic kidney disease (ADPKD).
- Recommendation to discontinue Samsca in patients with symptoms of liver injury.

The manufacturer of Samsca, Otsuka American Pharmaceutical, Inc., issued a Dear Health Care Provider letter on the potential risk of liver injury on January 22, 2013**.** FDA is reviewing the information from clinical trials of patients with ADPKD and will update the public on the risk of liver injury with Samsca if more information becomes available.

FACTS about Samsca (tolvaptan)

- A selective vasopression V2-receptor antagonist indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia [serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid

restriction], including in patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

- Samsca was approved with a boxed warning that mandates drug initiation and re-initiation should entail close monitoring of serum sodium in a hospital setting. Too rapid correction of hyponatremia can cause osmotic demyelination syndrome which can cause neurological changes and result in coma or death.

- From approval in May 2009 through February 2013, there were approximately 16,000 prescriptions dispensed and 4,500 patients who received a prescription for Samsca (tolvaptan) from U.S. outpatient retail pharmacies.[2] According to sales distribution data, sales to outpatient retail pharmacies accounted for approximately 40% of tolvaptan sales; 41% was distributed to non-retail pharmacies, and 18% to mail-order/specialty pharmacies during this time.[3]

Additional Information for Patients

- Samsca may cause liver problems, including life-threatening liver failure.

- Contact your health care professional right away if you take Samsca and experience any of these signs and symptoms of liver problems:

    - Loss of appetite, nausea, vomiting

    - Fever, feeling unwell, unusual tiredness

    - Itching

    - Yellowing of the skin or the whites of the eyes (jaundice)

    - Unusual darkening of the urine

    - Pain or discomfort in the right upper abdomen, where the liver is located

- Discuss any questions or concerns about Samsca with your health care professional.

- Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Additional Information for Health Care Professionals

- Samsca treatment should be stopped if the patient develops signs of liver disease.

- Limit the duration of Samsca treatment to 30 days or less.

- Avoid use of Samsca in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired.
- Report adverse events involving Samsca to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Data Summary

Samsca (tolvaptan) was approved in May 2009 for the treatment of clinically significant euvolemic and hypervolemic hyponatremia. Patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response before subsequently receiving Samsca in the outpatient setting.

Tolvaptan is being studied for another indication: delay in progression of renal disease in adult patients with autosomal dominant polycystic kidney disease (ADPKD).1 Three cases of serious liver injury attributed to tolvaptan were observed in a placebo-controlled trial in ADPKD and its open-label extension study, indicating the potential for the drug to cause liver injury that could progress to liver failure. In addition, tolvaptan was associated with an increased incidence of ALT elevations greater than three times the upper limit of normal: 42 subjects out of 958 (4.4%) in the tolvaptan group, compared to five subjects out of 484 (1.0%) in the placebo group. The serious liver injury cases were consistent with Hy's law. Hy's law is a prognostic indicator that FDA follows to evaluate the potential for drug-induced severe liver injury and typically refers to significant elevations of liver enzymes with concomitantly elevated bilirubin where etiologies other than the drug have been ruled out. See Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Final, July 2009. In the ADPKD trials, the earliest case of severe liver injury was observed three months after initiation of tolvaptan.

Analysis of safety information in the clinical trials that supported the hyponatremia indication (and in other populations such as those with heart failure) did not demonstrate hepatotoxicity. However, the controlled hyponatremia trials were of short duration—about 30 days. Although FDA has received spontaneous postmarketing reports of elevated liver enzymes and other liver events in patients taking tolvaptan, these reports are difficult to interpret because many of the patients had underlying disease that can be associated with elevated liver enzymes or liver injury (cirrhosis, heart failure, or cancer). Based on the cases of liver injury in patients participating in the ADPKD trials, FDA worked with the manufacturer to revise the Samsca drug label to include the above information, to reduce the potential for serious liver injury.

References

1. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease, *NEJM* 2012; 367: 2407-18.

2. SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT) Databases. May 2009-February 2013. Extracted April 9, 2013.

3. IMS Health, IMS National Sales Perspectives™ Database. May 2009-February 2013. Extracted April 9, 2013.