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26th March 2012

Direct Healthcare Professional Communication on the risk of increases in serum sodium with tolvaptan (Samsca) which are too rapid.

Dear Healthcare Professional

This letter is sent in agreement with the European Medicines Agency (EMA) to inform you on the risks of too rapid increases in serum sodium when using tolvaptan and how to minimise the risk.

Summary

- **Increases in serum sodium which are too rapid can be harmful and cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death.**

- **Close monitoring of serum sodium during tolvaptan treatment is recommended, especially in patients with very low serum sodium (<120 mmol/L) at baseline or in those at high risk of demyelination syndromes, for example those with hypoxia, alcoholism or malnutrition.**

- **Sodium correction that exceeds 6 mmol/L during the first 6 hours of administration or 8 mmol/L during the first 6-12 hours may be too rapid; in such patients close monitoring of serum sodium and administration of hypotonic fluid are recommended.**

- **Tolvaptan treatment should be interrupted or discontinued and followed by administration of hypotonic fluid if the increase in serum sodium is too rapid (i.e. if it exceeds 12 mmol/L in 24 hours, or 18 mmol/L in 48 hours).**

- **Co-administration of tolvaptan with medicines with a high sodium content or other treatments for hyponatraemia is not recommended.**

Further information on the safety concern

Tolvaptan (Samsca) is indicated for the treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Treatment with tolvaptan increases serum sodium which is the desired therapeutic effect. However, there have been reports of neurological sequelae in patients treated with tolvaptan where the correction of serum sodium has exceeded the suggested rate.

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The product information for tolvaptan (Samsca) has been updated with information on the risk of increases in serum sodium levels which are too rapid (see next section).

Further recommendations to healthcare professionals

- In patients at higher risk of demyelination syndromes, for example those with hypoxia, alcoholism or malnutrition, the appropriate rate of sodium correction may be lower than that in patients without risk factors; these patients should be very carefully managed.
- Co-administration of tolvaptan with any other treatment for hyponatraemia, and medications that increase serum sodium concentration, is not recommended. These patients may be at higher risk for developing rapid correction of serum sodium during the first 1-2 days of treatment due to potential additive effects. Therefore if co-administration is essential then these patients should be managed very cautiously.
- In addition, patients with very low serum sodium levels at baseline (<120 mmol/L) should be closely monitored during tolvaptan treatment.

Reporting suspected adverse drug reactions with the use of Samsca®

As a reminder, there is a need to report any suspected adverse reactions in accordance with the national spontaneous reporting system.

Please remember that any suspected adverse reactions following the use of tolvaptan (Samsca) should be reported to the Irish Medicines Board in accordance with the national spontaneous reporting system http://www.imb.ie/EN/Safety--Quality/Online-Forms.aspx.

Any adverse events associated with the use of Samsca® (tolvaptan) may also be reported to:

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Or email med.affairs@otsuka-europe.com

Communication Information

For further information on Samsca® please contact Otsuka on +44 (0) 1895 207100.

Yours faithfully

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