

TOLVAPTAN tablets (Samsca®) for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

The Pan Mersey Area Prescribing Committee recommends the prescribing of TOLVAPTAN tablets (Samsca®), by specialists only, for the treatment of hyponatraemia secondary to SIADH due to any cause

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Tolvaptan should only be initiated by a consultant endocrinologist. Prescribing should be retained by the specialist in secondary care.

Tolvaptan (Samsca®) is a third line option for treating hyponatraemia secondary to SIADH due to any cause only if:

- > Fluid restriction has been unsuccessful or is inappropriate, **and**
- > Treatment with demeclocycline has been unsuccessful or is inappropriate.

Tolvaptan (Samsca®) for the treatment of hyponatraemia secondary to SIADH in cancer patients in whom chemotherapy is being delayed due to their hyponatraemia will continue to be funded in line with [NHS England guidance](#).

Tolvaptan (Jinarc®) for treating autosomal dominant polycystic kidney disease should continue to be used in accordance with current [Pan Mersey guidance](#) and [NICE TA358](#).

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Effectiveness

Tolvaptan is a selective vasopressin V2-receptor antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V2-receptor of the distal portions of the nephron. Tolvaptan affinity for the human V2-receptor is 1.8 times that of native AVP^[1]. Two pivotal, double-blind, placebo-controlled, clinical trials examined the efficacy of tolvaptan; Study of Ascending Levels of Tolvaptan in hyponatraemia 1 and 2 (euvoalaemic patients were studied in SALT-1 and hypervolaemic patients in SALT-2). Patients had a variety of underlying aetiologies (heart failure, cirrhosis, SIADH). The primary endpoint was the change in average daily area under the curve for the serum sodium concentration from baseline to day 4 and the change from baseline to day 30. Tolvaptan was superior to placebo for both periods and in both studies regardless of baseline serum sodium or underlying cause (day 4 normalisation of serum sodium in 49% vs. 11% of patients; day 30 normalisation of serum sodium in 60% vs. 27% of patients)^[2]. The long-term safety and efficacy of tolvaptan was assessed in the Safety and sodium Assessment of Long-term Tolvaptan With hyponatraemia (SALTWATER) trial (an open-label extension of the SALT-1 and SALT-2 trials). Improvements in serum sodium were maintained throughout the 106 week study^[3].

Cost

The NHS Drug Tariff price of tolvaptan (Samsca®) is £89.62 per tablet (for both the 15mg and 30mg strength) and £53.77 per tablet (for the 7.5mg strength) - including VAT. Treatment duration varies between patients but two recent reviews reported an average course length of 3 or 4 days^[4, 5]. This equates to a cost of approximately £269 to £359 per course assuming a daily dose of 15mg or 30mg. Expenditure across the Pan Mersey region hospitals between March 2018 and February 2019 was approximately £16000.

Prescribing information

The initial starting dose of tolvaptan is 15mg once daily, although a lower starting dose of 7.5mg once daily can be considered. Tolvaptan should be titrated if necessary up to a maximum of 60mg once daily. Average course length is 3 or 4 days

Regular monitoring of weight changes, fluid status, serum sodium and serum osmolality is necessary. Monitoring of urine osmolality should also be considered if serum osmolality is abnormal.

Patients should maintain an adequate fluid intake whilst on tolvaptan to prevent dehydration.

Safety

Tolvaptan is contraindicated in anuria, volume depletion, hypovolaemic hyponatraemia, hypernatraemia and in patients who cannot perceive thirst.

Fluid and electrolyte status must be monitored in patients taking tolvaptan as treatment can result in severe dehydration and electrolyte disturbances. Patients should maintain an adequate fluid intake whilst on tolvaptan to prevent dehydration. Tolvaptan has been associated with over-rapid correction of hyponatraemia risking serious neurological events; always seek endocrinology input in patient management – see [MHRA alert](#).

There is a risk of liver injury associated with the use of tolvaptan. Liver function testing is recommended in patients presenting with symptoms that may indicate liver injury – see [MHRA alert](#).

The majority of side effects relate to tolvaptan's effect on sodium and water homeostasis with the most commonly reported adverse effects of treatment being thirst, dry mouth and pollakiuria. Tolvaptan may also cause hyperglycaemia. For a full list of adverse effects, consult the [summary of product characteristics](#).

Patient factors

For patients at risk of overly rapid correction of sodium (e.g. patients with oncological conditions, very low baseline serum sodium, those taking diuretics, or sodium supplementation), a starting dose of 7.5 mg should be considered.

No dose adjustment is required in patients with mild or moderate renal impairment although tolvaptan has not been studied in patients with severe renal failure. No information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing must be managed cautiously. No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A or B).

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Implementation notes

Tolvaptan is PBR-excluded and should only be initiated by a consultant endocrinologist. Prescribing and ongoing monitoring should be retained by the specialist in secondary care with drug cost recharged to the CCG.

References

1. Electronic Medicines Compendium. Samsca 15mg tablets summary of product characteristics. [internet] October 2018. [accessed 29th January 2019]. Available from: <https://www.medicines.org.uk/emc/product/6635/smpc>
2. Schrier, RW *et al.* Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatraemia. *The New England Journal of Medicine*, 2006: Vol 355, p2099-2112. <https://www.nejm.org/doi/full/10.1056/nejmoa065181>
3. Berl, T *et al.* Oral tolvaptan is safe and effective in chronic hyponatremia. *Journal of the American Society of Nephrology*, 2010: Vol 21, No. 4, p705-712. <https://doi.org/10.1681/ASN.2009080857>
4. Tzoulis, P *et al.* Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion. *Clinical Endocrinology*, 2015: Vol 84, No. 4, p620-626. <https://doi.org/10.1111/cen.12943>
5. Rajendran, R *et al.* Vasopressin receptor antagonist in the treatment of the syndrome of inappropriate antidiuretic hormone in general hospital practice. *Endocrine Journal*, 2012: Vol 59, No. 10, p903-909. <https://doi.org/10.1507/endocrj.EJ12-0171>