# New drugs

## Tolvaptan

**Approved indication: hyponatraemia**
**Samsca (Aspen)**
**15 mg and 30 mg tablets**
**Australian Medicines Handbook section 10.6.2**

Hyponatraemia is a common electrolyte abnormality. It can be associated with heart failure, cirrhosis and the syndrome of inappropriate antidiuretic hormone secretion (see Aust Prescr 2011;34:42-5).

Unless there is hypovolaemia, hyponatraemia is usually treated with fluid restriction. Additional treatment is needed if severe hyponatraemia persists and the patient remains symptomatic.

A new approach is to target the action of antidiuretic hormone (vasopressin). Tolvaptan is an antagonist at the vasopressin $V_2$ receptor. By blocking the binding of antidiuretic hormone to the receptor, tolvaptan increases the excretion of water. As there is no significant change in sodium excretion, the serum concentration of sodium increases.

The serum sodium begins to rise 2–4 hours after an oral dose, with a peak effect at 4–8 hours. Treatment is given once a day, starting at 15 mg. The dose can be increased, but the effect on serum sodium does not increase beyond 60 mg daily.

Tolvaptan is mainly metabolised by cytochrome P450 3A. Co-administration with inducers or inhibitors of this enzyme should be avoided. The tablets should not be taken with grapefruit juice. No dose adjustment has been recommended for patients with liver disease. Anuria, hypovolaemia and an inability to sense thirst are contraindications.

In a small open-label trial, tolvaptan was compared to fluid restriction in 28 inpatients with euvolaemic or hypervolaemic hyponatraemia. These patients had serum sodium concentrations below 135 mmol/L. There was a significant increase in serum sodium four hours after the first dose of tolvaptan. By day four of treatment serum sodium was normal in 50% of the tolvaptan group. It took until day eight for sodium to return to normal in 50% of the fluid restriction group.[1]

Two double-blind trials then randomised 225 patients to take tolvaptan and 223 to take placebo for up to 30 days. The patients were euvolaemic or hypervolaemic with sodium concentrations below 135 mmol/L. Approximately half the patients only had mild hyponatraemia (130–134 mmol/L). The sodium concentration increased significantly more with tolvaptan than with placebo. In the tolvaptan groups, 40–55% of patients had a normal serum sodium by the fourth day of treatment, compared with 11–13% of the placebo groups. By day 30, the respective figures were 53–58% and 25%.[2]

The most common adverse effects of tolvaptan were thirst and dry mouth. Serious adverse events include dehydration, acute renal failure and ascites.[2] As increasing the excretion of water will raise the concentration of potassium, as well as sodium, some patients will be at risk of hyperkalaemia.

Acute severe hyponatraemia is a medical emergency, but tolvaptan has not been studied in this setting. It is not recommended for use with hypertonic saline.

If the serum sodium rapidly rises there is a risk of cerebral demyelination. Fluid restrictions should generally be lifted when tolvaptan is started to reduce the chance of a rapid rise. The restrictions can be resumed after treatment, especially as serum sodium will tend to fall when tolvaptan is stopped.[2] In view of the need to titrate the dose and monitor electrolytes, tolvaptan should be started in hospital.

While tolvaptan can correct the serum sodium in a proportion of patients with hyponatraemia, its clinical role is unclear. It is important to manage the underlying causes of hyponatraemia. Although hyponatraemia is associated with increased mortality in patients with cirrhosis, the safety and efficacy of tolvaptan has not been established in this group. There is some evidence that the drug increases the risk of gastrointestinal bleeding in patients with cirrhosis. The efficacy of tolvaptan in heart failure is also uncertain. It did not significantly reduce the length of hospital stay for patients with heart failure and hyponatraemia.[3]

[T] manufacturer provided the product information

### REFERENCES *†A

1. Gheorghiade M, Gottlieb S, Udelson JE, Konstam MA, Czerwiec F, Ouyang J, et al; Tolvaptan Investigators. Vasopressin V2 receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. Am J Cardiol 2006;97:1064-7.
2. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al; SALT Investigators. Tolvaptan, a selective oral vasopressin $V_2$-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-112.
3. Cyr PL, Slawsky KA, Olchanski N, Krasa HB, Goss TF, Zimmer C, et al. Effect of serum sodium concentration and tolvaptan treatment on length of hospitalization in patients with heart failure. Am J Health Syst Pharm 2011;68:328-33.

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Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)