New Medicine Assessment

TOLVAPTAN

Recommendation: RED for the following indications:

Treatment of hyponatremia in adults, secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), only if:

- Treatment is initiated, titrated and monitored in hospital, by a specialist experienced in the treatment of SIADH, and
- Fluid restriction has been unsuccessful or is inappropriate, and
- Treatment with demeclocycline has been unsuccessful or is inappropriate.

Summary of supporting evidence:

- Tolvaptan has been studied for nearly 30 years
- Two large multi-centre, randomised, double-blind, placebo-controlled, efficacy and safety studies of the effects of titrated oral tolvaptan tablets in patients with hyponatremia have been conducted
- There is evidence of an effect on the serum sodium levels and the secondary parameters including urine output, fluid intake and overall fluid balance
- Vasopressin receptor antagonists may reduce the length of hospital stay in some patients
- Tolvaptan dosing is once daily, compared to multiple daily dosing for demeclocycline
- Tolvaptan is not suitable for acute situations where there is an urgent requirement to raise sodium
- Tolvaptan has complex dose titration and monitoring requirements, including fluid and electrolyte balance
- Failure to correct hyponatremia can lead to permanent neurologic damage, as can over rapid correction of serum sodium causing osmotic demyelination.
- Data for other interventions in hyponatremia is largely absent
- There are concerns around the potential for liver injury caused by tolvaptan use (MHRA alert)
  The FDA recommend that tolvaptan should not be used for more than 30 days due to reports of potentially fatal liver injury in patients with autosomal dominant polycystic kidney disease
- Tolvaptan is teratogenic; women of childbearing potential must use effective contraception during tolvaptan treatment
- Several European clinical societies do not recommend vasopressin receptor antagonists as they consider the risk/benefit ratio to be negative, although this recommendation is from 2014
- High cost per dose, length of treatment variable
- Pan Mersey APC and GMMMG both recommend the prescribing of tolvaptan for hyponatraemia resulting from SIADH

Details of Review

Name of medicine (generic & brand name)**:**[1]

Tolvaptan (Jinarc, Samsca, Tolvaptan Teva)

Strength(s) and form(s):1

Tablets

Jinarc 15mg, 30mg, 45mg, 60mg, 90mg

Samsca 7.5mg, 15mg, 30mg

Tolvaptan Teva 15mg, 30mg, 45mg, 60mg, 90mg

Dose and administration:

Samsca[1]

Oral, preferably in the morning, swallowed whole with water.

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, treatment with Samsca has to be initiated in hospital.

Initiate at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium.

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

During titration, patients must be monitored for serum sodium and volume status. In case of inadequate improvement in serum sodium levels, other treatment options have to be considered, either in place of or in addition to tolvaptan. Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium. For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels must be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatremia, the treatment duration is determined by the underlying disease and its treatment. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatremia is no longer a clinical issue.

Samsca must not be taken with grapefruit juice.

Jinarc and Tolvaptan Teva formulations are licensed to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease, and therefore fall out of the scope of this review.

BNF therapeutic class / mode of action:

Tolvaptan is a vasopressin V2-receptor antagonist.[2]

Licensed indication(s):

Samsca (tolvaptan) is indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Proposed use (if different from, or in addition to, licensed indication above):

Treatment of hyponatremia in adults, secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

For commissioning purposes, we will be reviewing its use for patients **not** requiring chemotherapy.

NB. Tolvaptan for hyponatraemia secondary to SIADH in **patients requiring cancer chemotherapy** is commissioned by NHS England according to their Clinical Commissioning Policy. Chemotherapy requires

patients to be well hydrated. However, an increase in fluid intake can cause hyponatraemia which may delay the start of chemotherapy.

Course and cost:

Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatremia is no longer a clinical issue.[1]

Tolvaptan (Samsca) 7.5mg = £448.08 for 10 tablets (drug tariff Nov 2022)

15mg = £746.80 for 10 tablets (NHS dm+d browser)

30mg = £746.80 for 10 tablets (NHS indicative price, BNF)

Cost per dose approx. £45 - £150.

Current standard of care/comparator therapies:

SIADH

- Fluid restriction and treat underlying cause
- Intravenous hypertonic saline (3% sodium chloride solution)[3]
- Furosemide may be used in addition to hypertonic saline, especially if the patient is at risk for volume overload[3]
- If there is no clear cause for SIADH following initial investigations, CT chest/abdomen/pelvis and MRI head may be arranged to exclude underlying malignancy[4]
- Demeclocycline hydrochloride - thought to act by directly blocking the renal tubular effect of antidiuretic hormone[5]
- Tolvaptan (a vasopressin V2-receptor antagonist) is indicated in adults for the treatment of hyponatremia secondary to SIADH. Treatment should be initiated in hospital or under specialist supervision[4]

Relevant NICE guidance:

Tolvaptan for treating autosomal dominant polycystic kidney disease [TA358] 2015

Background and context

Syndrome of inappropriate antidiuretic hormone ADH release (SIADH) is a condition defined by the unsuppressed release of antidiuretic hormone (ADH) from the pituitary gland or nonpituitary sources or its continued action on vasopressin receptors. SIADH is characterised by impaired water excretion leading to hyponatremia with hypervolemia or euvolemia.[6]

Cerebral oedema is a potentially life-threatening complication of severe and/or acute hyponatraemia. Complications of chronic hyponatraemia include increased risk of falls, bone fractures, and osteoporosis. Failure to correct hyponatremia can lead to permanent neurologic damage, as can over rapid correction.[4]

Hyponatremia is initially managed by investigating the underlying cause and treating using a balance of fluid restriction and hypertonic fluids. Further options include furosemide, demeclocycline and tolvaptan.

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. Following single oral doses of 7.5 to 60 mg, 24-hour urine volume increased dose dependently with daily volumes ranging from 3 to 9 litres. For all doses, urine excretion rates returned to baseline levels after 24 hours.[1]

Due to reports of potentially fatal liver injury in patients with autosomal dominant polycystic kidney disease, tolvaptan should not be used for more than 30 days, and it should be avoided in patients with underlying liver disease including cirrhosis. The drug should be discontinued immediately in patients with signs or symptoms of liver injury. Close monitoring, especially in the first 24 hours of oral therapy, is required. The concern is overcorrection of serum sodium. Fluid restriction should be removed because polyuria commonly occurs.[3]

Summary of evidence

Summary of efficacy data in proposed use:

European Medicines Agency (2009)[7]

A number of disorders, including congestive heart failure (CHF), liver cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion, are associated with increased AVP secretion. Increased AVP levels lead to excessive water retention accompanied by electrolyte imbalances, in particular hyponatraemia.

The clinical development of tolvaptan was initiated in 1994 with early healthy subject trials conducted in Japan and has since been investigated extensively in hyponatraemia and heart failure patients.

The 2 pivotal studies in the hyponatraemia programme were SALT 1 (Multi-center, randomised, double-blind, placebo-controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia) and SALT 2 (International, multi-center, randomised, double-blind, placebo controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia).

In both trials, the subjects enrolled had non-acute euvolemic or hypervolemic hyponatraemia, defined as serum sodium <135 mEq/L (mmol/L) irrespective of aetiology (including CHF, liver disease or SIADH). Among other exclusion criteria, subjects were excluded if they were hypovolemic; had hyponatraemia due to head trauma, post-operative state, medicinal therapy that could be safely withdrawn (e.g. thiazide diuretics), laboratory artefacts or psychogenic polydipsia; received other treatment for hyponatraemia (demeclocycline, lithium carbonate or urea); or required intravenous saline for severe hyponatraemia.

Subjects are initially randomized to tolvaptan 15 mg once daily or placebo. The dose was individually optimised for each subject: the initial dose of tolvaptan could be increased to 30 mg and then 60 mg, if the response to the previous dose was inadequate (i.e. if the change in serum sodium level from the previous measurement was < 5 mEq/L and if the sodium concentration remained < 135 mEq/L).

These two pivotal phase 3 trials were identical in design. The primary objective was to demonstrate that tolvaptan is a safe, effective, and useful agent for achieving and maintaining increased serum sodium for the treatment of non-hypovolemic hyponatraemia arising from a variety of aetiologies over a 30-day treatment period in both trials. The primary endpoint was the change from baseline in mean daily AUC of

serum sodium concentration.

The pooled population across both trials of patients with SIADH/Other was 42.2%. Serum sodium normalized (>135 mEq/L) in more than 50% of subjects treated with tolvaptan. The results were similar in subjects with mild and severe hyponatraemia. The biggest difference compared to placebo was seen for the SIADH/Other subjects. The overall results suggests that tolvaptan favourably influences the sodium and fluid balance across aetiologies and across varied volemic states. The urine output was consistently and statistically significantly greater in the tolvaptan group than the placebo group in the pooled analysis, regardless of aetiology.

In the hyponatraemia population, tolvaptan undoubtedly improves serum sodium balance for the duration of therapy and prevents progressive lowering of sodium. There is clear evidence of an effect on the serum sodium levels and the secondary parameters including urine output, fluid intake and overall fluid balance.

The central issue therefore is whether "correction of hyponatraemia offers clinically relevant effect" and this has been shown for the SIADH population.

Cochrane (2018)[8]

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia

This review aimed to 1) look at the benefits and harms of interventions for chronic non-hypovolaemic hypotonic hyponatraemia when compared with placebo, no treatment or head-to-head; and 2) determine if benefits and harms vary in absolute or relative terms dependent on the specific compound within a drug class, on the dosage used, or the underlying disorder causing the hyponatraemia.

We identified 35 studies, enrolling 3429 participants. Twenty-eight studies (3189 participants) compared a vasopressin receptor antagonist versus placebo, usual care, no treatment, or fluid restriction.

In adults with chronic, non-hypovolaemic hypotonic hyponatraemia, vasopressin receptor antagonists have uncertain effects on death at six months (15 studies, 2330 participants: RR 1.11, 95% CI 0.92 to 1.33) due to risk of selective reporting and serious imprecision; and on health-related quality of life because results are at serious risk of performance, selective reporting and attrition bias, and suffer from indirectness related to the validity of the Short Form Health Survey (SF-12) in the setting of hyponatraemia.

Vasopressin receptor antagonists may reduce hospital stay (low certainty evidence due to risk of performance bias and imprecision) (3 studies, 610 participants: MD -1.63 days, 95% CI -2.96 to -0.30), and may make little or no difference to cognitive function (low certainty evidence due to indirectness and imprecision).

Vasopressin receptor antagonists probably increase the intermediate outcome of serum sodium concentration (21 studies, 2641 participants: MD 4.17 mmol/L, 95% CI 3.18 to 5.16), corresponding to two and a half as many people having a 5 to 6 mmol/L increase in sodium concentration compared with placebo at 4 to 180 days (moderate certainty evidence due to risk of attrition bias) (18 studies, 2014 participants: RR 2.49, 95% CI 1.95 to 3.18). But they probably also increase the risk of rapid serum sodium correction - most commonly defined as > 12 mmol/L/d (moderate certainty evidence due to indirectness) (14 studies, 2058 participants: RR 1.67, 95% CI 1.16 to 2.40) and commonly cause side-effects such as thirst (13 studies, 1666 participants: OR 2.77, 95% CI 1.80 to 4.27) and polyuria (6 studies, 1272 participants): RR 4.69, 95% CI 1.59 to 13.85) (high certainty evidence).

The potential for liver toxicity remains uncertain due to large imprecision. Effects were generally consistent across the different agents, suggesting class effect. Data for other interventions such as fluid restriction, urea, mannitol, loop diuretics, corticosteroids, demeclocycline, lithium and phenytoin were largely absent.

In people with chronic hyponatraemia, vasopressin receptor antagonists modestly raise serum sodium concentration at the cost of a 3% increased risk of it being rapid. To date there is very low certainty evidence for patient-important outcomes; the effects on mortality and health-related quality of life are unclear and do not rule out appreciable benefit or harm; there does not appear to be an important effect on cognitive function, but hospital stay may be slightly shorter, although available data are limited. Treatment decisions must weigh the value of an increase in serum sodium concentration against its short-term risks and unknown effects on patient-important outcomes.

CADTH (2013)[9]

The Canadian Drug Expert Committee (CDEC) recommends that tolvaptan not be listed.

Reasons for the Recommendation:

1. Two placebo-controlled randomized controlled trials (RCTs) demonstrated that tolvaptan significantly improved serum sodium levels in patients with heart failure and non-hypovolemic hyponatremia; however, there was insufficient evidence that treatment with tolvaptan provides clinical benefits for mortality, morbidity, or reduced length of hospitalisation relative to appropriate alternative treatments or placebo.

2. Tolvaptan was not considered to be cost-effective in patients with heart failure and non-hypovolemic hyponatremia and there was insufficient pharmacoeconomic evidence to evaluate the use of tolvaptan for the treatment of non-hypovolemic hyponatremia in other patient populations.

Spasovski et al (2014)[10]

European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP) Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia.

Although vasopressin receptor antagonists do increase serum sodium, the guideline development group judged that based on current evidence, these drugs cannot be recommended. Indeed, the risk benefit ratio seems to be negative: there is no proven outcome benefit aside from increase in serum sodium concentrations, while there are increasing concerns on safety. The most prominent safety related factor is the increased risk for overly rapid correction of hyponatraemia. As this risk is greatest in patients with profound hyponatraemia, the guideline development group wanted to recommend against the use of vasopressin receptor antagonists in this specific patient group. In addition, our concern around the toxicity profile of these compounds was increased by reports from the U.S. Food and Drug Administration warning for hepatotoxicity associated with the use of high tolvaptan doses in autosomal dominant polycystic kidney disease.

Lee et al (2022)[11]

Korean Society of Nephrology

Recommendation 6. We suggest treatment with vaptans in SIAD patients with moderate to severe hyponatremia (B, low).

In patients with SIAD, the standard treatment is the restriction of free water because of water retention. The following can be considered second-line treatment: a combination of oral sodium chloride (NaCl) and loop diuretics or vaptans (Recommendation 6).

Remarks: 1. There is no direct comparison of vasopressin receptor antagonists with loop diuretics in patients with SIAD. We compared the effects of vasopressin receptor antagonists with water restriction or placebo. 2. Vaptans have a beneficial effect on normalization of SNa in SIAD patients compared with water restriction or placebo. 3. Vaptans do not increase the risk of overcorrection of hyponatremia in SIAD patients compared with water restriction or placebo. 4. Vaptans do not improve survival in SIAD patients compared with water restriction or placebo.

Chatzimavridou-Grigoriadou et al (2021)[12]

Christie Hospital NHS Foundation Trust, Manchester

Retrospective evaluation in a tertiary cancer centre to assess the safety and efficacy of low-dose tolvaptan (7.5 mg) for hospitalized, adult patients with hyponatremia due to syndrome of inappropriate antidiuresis (SIAD), and coexisting malignancy.

Fifty-five patients were included in the final analysis and received at least 1 dose of 7.5 mg of tolvaptan. All the included patients had a diagnosis of SIAD. Effectiveness of tolvaptan was measured using the following criteria: the average sNa rise at 24, 48, and 72 hours, the proportion of patients with sNa > 130 mmol/L within a week since the administration of the first dose of tolvaptan and the percentage of patients with a sNa rise of ≥5 mmol/L in 48 hours.

Severe hyponatremia (sNa < 125 mmol/L) at baseline was present in 90.9% of the patients (n = 50) and moderate hyponatremia (sNa 125-129 mmol/L) in 9.1% (n = 5). Baseline sNa (mean ± SD) was 117.9 ± 4.6 mmol/L, with a lowest value of 108 mmol/L.

The rate of sNa correction in the first 24 hours of treatment was higher among participants that continued receiving demeclocycline after tolvaptan was administered, although the difference did not reach the level of statistical significance (median [quantiles] 14 [9.5-15.5] mmol/L versus 8 [6.8-11] mmol/L, P = .08). While in the over-rapid correction cohort demeclocycline was appropriately discontinued only in 60% of the participants, the respective percentage was 91.7% in the remaining participants, P = .047. The rate of sNa correction in the first 24 hours of treatment was also significantly higher among 5 participants whose fluid restriction was not eased prior to tolvaptan initiation, compared with 30 participants where fluid restriction was appropriately eased (median [quantiles]: 14 [9-16] mmol/L versus 8 [5-11] mmol/L, P = .036). However, data were missing on whether fluid restriction was eased in 8 participants. Thirty-nine patients (70.9%) reached a sNa ≥ 130 mmol/L within 1 week from initiation of treatment. Forty-eight patients (87.3%) had a rise in sNa of ≥5 mmol/L within 48 hours.

Univariate regression analyses revealed that lower creatinine was predictive of higher correction rate of sNa within the first 24 hours (P = .003).

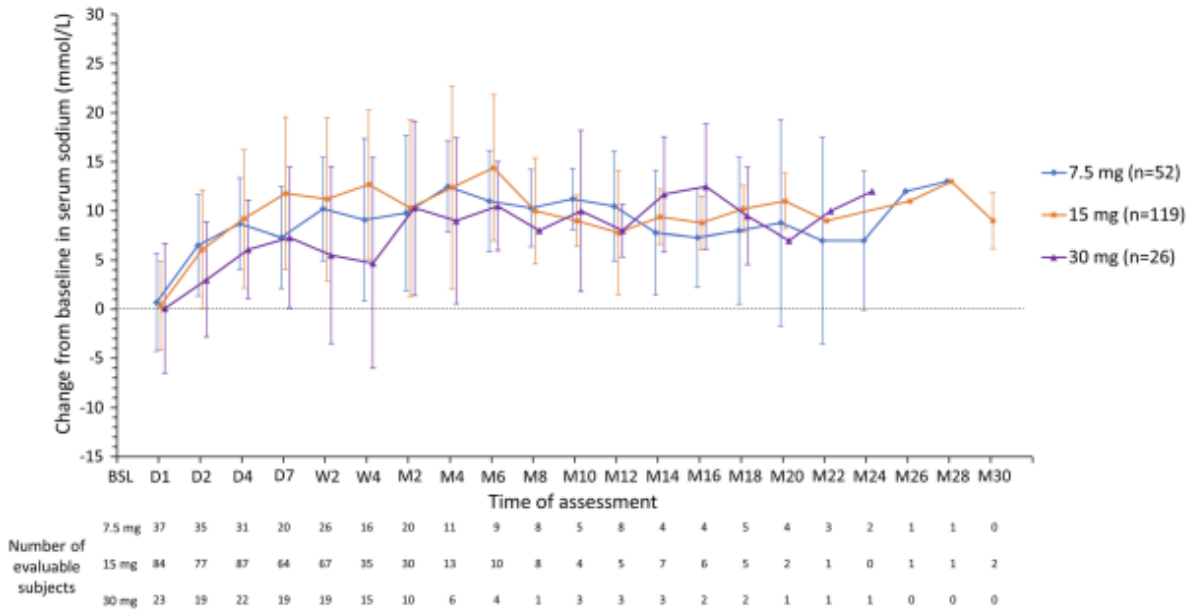
Use of tolvaptan at an initial dose of 7.5 mg is clinically effective. However, even this lower dose is associated with a risk of over-rapid correction of hyponatremia. Our findings also highlight the need to avoid concurrent administration of demeclocycline and/or fluid restriction with tolvaptan, which further increases the risk of over-rapid correction. Considering the significant proportion of patients experiencing over-rapid correction, we suggest tolvaptan should be administered in only selected cases with specialist input (for instance from endocrine or nephrology team) and where other alternatives (eg, urea) have been considered, as part of a structured clinical pathway.

Estilo et al (2021)[13]

This was a prospective, observational, multinational, post-authorisation phase 4 pharmacovigilance study in seven European countries. Hospitalized patients were enrolled who received tolvaptan for hyponatremia associated with SIADH. A total of 65 hospital sites participated in the study, including 48 active sites that enrolled 252 patients from 2 November 2010 to 15 November 2012.

The mean duration of tolvaptan exposure was 139.4 (SD 239.68) days, with a median treatment length of 18.5 (range of 1–1130) days. The maximum daily dose ranged from 3.75 to 60.0 mg/day. A daily dose of 15 mg was the dose administered to the greatest number of patients (189/252; 75.0%). The most frequent SIADH aetiology was tumour (107/252; 42.5%), followed by idiopathic disease (66/252; 26.2%) and drug-induced (22/252; 8.7%).

Mean change from baseline in serum sodium over time is shown in the graph below, for patients grouped according to the dose they received during their stable treatment phase (7.5, 15, or 30 mg/day). Increases from baseline in serum sodium were comparable across stable tolvaptan dose categories; no dose relationship was discernible.



Mean (SD) change from baseline in serum sodium (mmol/l) in patients grouped by stable daily tolvaptan dose received. Patients who did not enter a stable treatment phase were grouped according to their most used dose. Data are not shown for patients who received tolvaptan 3.75 mg less than daily, 3.75 mg/day, 7.5 mg less than daily, 15 mg less than daily, 45 mg/day, or 60 mg/day as a stable daily dose, given the small numbers of patients receiving a specific dose within each category. *BSL* baseline, *D* day, *M* month, *SD* standard deviation, *W* week

Limitations of this real-world study include data collection, which was dependent on local standards of practice rather than prespecified visit and assessment schedules, and the lack of a control group or randomised design. No standardised data-reporting protocols were used; rather, the investigators simply recorded the choices made for patient care.

Morris et al (2018)[14]

Multi-centre retrospective review of medical records to identify patients treated with oral tolvaptan between 2010 and 2015. The study population consisted of hospitalised adult patients 18 years or older treated with an initial daily dose of 15 mg of tolvaptan. Eligible patients had a diagnosis of moderate to severe hypo-osmolal hyponatremia, defined as serum sodium concentration ≤ 130 mEq/L and serum osmolality ≤ 280 mOsm/kg, caused by either SIADH, or by CHF. Each patient needed documented failure to correct hyponatremia despite 24 or more hours of free water restriction (≤1 L/d). To reduce the risk for rapid correction, fluid restriction was discontinued at the time of initiation of tolvaptan therapy.

The primary end point was absolute change in serum sodium concentration during the first 24 hours following the first dose of tolvaptan. Rapid correction of hyponatremia was defined as an increase in serum sodium concentration > 12 mEq/L after 24 hours of therapy.

In total, 28 patients with SIADH entered the analysis. A more rapid and greater increase in serum sodium concentration was observed in patients with SIADH compared with patients with CHF. The mean increase in serum sodium concentration at 24 hours after initiation of tolvaptan therapy was greater for the SIADH cohort compared to the CHF group: 8.3 ± 6.3 mEq/L versus 5.0 ± 3.7 mEq/L (P = 0.03). Rapid correction of hyponatremia (>12 mEq/L in 24 hours) occurred in 25% of patients with SIADH versus 3% of those with CHF (P < 0.001; Fig 2B). Within the SIADH group, the underlying cause of SIADH did not seem to influence the rate of correction. Five (17.9%) patients with SIADH received intravenous D5W solution as an attempt to revert a rapid correction of hyponatremia.

In the SIADH cohort, age and baseline values for serum sodium, serum osmolality, SUN (serum urea nitrogen concentration), serum creatinine, eGFRMDRD, and eGFRCKD-EPI significantly correlated with the magnitude of increase in serum sodium concentration during the first 24 hours of therapy. Unlike those parameters, no significant correlation was found between the initial 24-hour increase in serum sodium concentration and either body weight, body mass index, or baseline urine sodium, urine osmolality, serum

uric acid, or serum potassium value.

This study demonstrates that the rapidity of correction of hyponatremia due to SIADH with tolvaptan is significantly associated with lower serum sodium and lower SUN concentrations before initiation of therapy. When our cohort was divided according to baseline serum sodium and baseline SUN concentrations, those with both lower serum sodium and lower SUN concentrations carried higher risk for overly rapid correction. In such a patient population, a lower starting dose of 3.75 to 7.5 mg might be sufficient to adequately correct the hyponatraemic state, with lesser risk for rapid correction.

Berl et al. (2010)[15]

SALTWATER trial

At entry to SALTWATER, the number of patients who had normonatremia, mild hyponatremia, and more marked hyponatremia were 17 (15.3%), 59 (53.2%), and 35 (31.5%), respectively. Patients were distributed by their original causes of hyponatremia (congestive heart failure [CHF] 29.7%, cirrhosis 18.0%, and syndrome of inappropriate antidiuretic hormone secretion [SIADH]/other 52.3%.

Previous treatment with tolvaptan or placebo in SALT-1 and SALT-2 did not alter the long-term efficacy of tolvaptan in SALTWATER. After the initial titration period, mean serum sodium levels remained within the normal range throughout the subsequent >4-year treatment period.

In all patient subgroups, serum sodium levels declined by 7 days of withholding tolvaptan, indicating a need for continued tolvaptan therapy to maintain serum sodium normalisation in many patients. On drug discontinuation, the proportion of patients who declined by at least 3 mEq/L was 68%, and an equal proportion fell from 135 mEq/L to below this threshold of normal.

Summary of safety data:

MHRA (2014)[16]

A clinical trial in the USA investigating the potential use of tolvaptan in about 1400 patients with autosomal dominant polycystic kidney disease (ADPKD, an unlicensed indication) identified an increased risk of serious liver injury in adults assigned 120 mg tolvaptan daily (i.e. twice the maximum recommended daily dose in the licensed indication) compared with placebo.

In the ADPKD population, clinically significant increases in both serum alanine aminotransferase (ALT, >3 times the upper limit of normal [ULN]) and total bilirubin (>2 times ULN) were observed in three patients assigned tolvaptan and no patients assigned placebo. Furthermore, there were significant elevations to >3 times ULN for ALT (4.4% for tolvaptan vs 1.0% for placebo) and for serum aspartate aminotransferase (AST, 3.1% vs 0.8%, respectively). Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after discontinuation of tolvaptan and were not associated with fulminant liver failure, or with permanent liver injury or dysfunction.

Other clinical trials of tolvaptan for hyponatraemia, including those supporting the European-approved indication, did not show an increased incidence of liver injury compared with placebo. However, patients with hyponatraemia treated with tolvaptan were more likely to have elevations in total bilirubin or ALT than placebo. These data cannot exclude the possibility that patients with SIADH treated with tolvaptan for hyponatraemia are potentially at increased risk of liver injury.

Advice for healthcare professionals:

- tolvaptan is licensed only for the treatment of adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH) at a dose of 15–60 mg once a day
- patients taking tolvaptan who report symptoms that may indicate liver injury should receive prompt liver-function testing; these symptoms include fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice
- patients with liver enzyme abnormalities (such as elevations of ALT, AST, or bilirubin) should be investigated to exclude significant hepatotoxicity

Prescribers should stop tolvaptan treatment in patients if liver injury is suspected and use alternative appropriate treatment. Tolvaptan should not be restarted in patients unless the cause of the observed liver injury is definitively established to be unrelated to tolvaptan treatment.

FDA (2017)[17]

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). 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.

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 post marketing 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).

European Medicines Agency (2009)[7]

Tolvaptan has been investigated clinically in Japan since 1994 and in Europe and the US since 1996. The safety dataset consists of 3294 subjects treated with any dose of tolvaptan and 2738 subjects treated with placebo from a total of 14 clinical trials. The exposure of subjects to tolvaptan in the heart failure and hyponatraemia programme is adequately representative to assess the adverse event profile. Whether the size of the data set and duration of treatment (exposure) is adequate to assess mortality is questionable. Only ~800 subjects are exposed to tolvaptan for over 1 year and this considered to a limitation.

The following were the most frequent possibly related TEAEs: thirst, ~18% in tolvaptan group [~2.5% in SC group], dry mouth (8.5 vs. 2.1%), pollakiuria (frequent day time urination: 5.4 vs. 0.9%), fatigue (2.3 vs. 0.9%), polyuria (3.3% vs. 0.6% SC) and ventricular tachycardia (0.9% vs. 0.3% SC). Cardiac disorders occupied the highest frequency. Interestingly, hypokalaemia (6.3% T vs. 7.9% SC) upper abdominal pain (1.8 %T vs. 3.2% SC) and muscle spasms (2.9% T vs. 3.9% SC) were more frequent in the placebo group. Acute renal failure occurred in >2% of subjects in the overall population and was marginally higher in the placebo group (3.2%T vs. 4.1% SC).

Overall cardiac failure (15% for tolvaptan vs. 17% SC) and congestive cardiac failure (=12% in both) were the most common serious TEAEs. With the exception of pneumonia (2.6% for both groups), ventricular tachycardia (2.2% for tolvaptan and 1.8% for placebo), and acute renal failure (2.0% for tolvaptan and 2.7% for placebo), all other serious TEAEs were reported at frequencies less than 2%.

There are no major safety concerns related to tolvaptan except for the teratogenicity.

Estilo et al (2021)13

This was a prospective, observational, multinational, post-authorization phase 4 pharmacovigilance study in seven European countries.

In the 3.75 mg daily or less than daily dose group, 0 patients (0.0%) experienced TEAEs (there were only four patients in this group); in the 7.5 mg less than daily and 7.5 mg daily groups, 27/45 patients (60.0%) and 57/106 patients (53.8%), respectively, experienced TEAEs; in the 15 mg less than daily and 15 mg daily groups, 19/31 patients (61.3%) and 105/189 patients (55.6%), respectively, experienced TEAEs; in the 30 mg less than daily group no patient experienced any TEAEs (there were only three patients in this group); and in the 30 mg daily group 27/43 patients (62.8%) experienced TEAEs.

Regarding adverse event severity, there was no clear indication that higher daily tolvaptan doses were

associated with increased reporting of serious TEAEs.

TEAEs with a fatal outcome were experienced by 57 patients (22.6%), and a total of 105 events were reported. Regarding a potential causal relationship with tolvaptan, the physician considered the events with fatal outcome as not related to tolvaptan for 51 patients and to have an unknown relationship to tolvaptan for the other 6 patients.

A total of 62/252 patients (24.6%) experienced ≥1 episode of rapid correction of hyponatremia during the study. No event of osmotic demyelination syndrome was reported during the study.

A search for predefined preferred terms related to hepatic disorders identified nine cases.

Chatzimavridou-Grigoriadou et al (2021)[12]

Christie Hospital NHS Foundation Trust, Manchester

Retrospective evaluation in a tertiary cancer centre to assess the safety and efficacy of low dose tolvaptan (7.5 mg) for hospitalized, adult patients with hyponatremia due to syndrome of inappropriate antidiuresis (SIAD), and coexisting malignancy.

No adverse events were documented and there were no reported neurological signs or symptoms suggestive of central pontine myelinolysis. Nine patients out of 53 with available data regarding imaging, had an MRI head within a month following tolvaptan treatment. Only in 1 patient the scan was requested due to over-rapid sNa correction, whereas in the remaining 8 patients the scans were requested for reasons not related to tolvaptan treatment. Three out of the 8 patients did have a rise in sNa ≥ 12 mmol/L in 24 hours. None of these 9 scans were reported as central pontine myelinolysis.

Out of the 30 patients without liver metastases, 21 patients had no elevations in AST or bilirubin. Only 1 patient had an AST of 115 IU/L (range 5-45) with bilirubin of 25 (range 1-20 µmol/L) 4 months post tolvaptan, but at the time was also treated for rectal abscess and disease progression. In the remaining 8 patients, AST was <2 upper limit of normal with normal bilirubin and this recovered spontaneously.

Our current protocol advises urgent discussion with the endocrine team if ≥6 mmol/L rise in serum sodium within first 6 hours or ≥8 mmol in 12 hours occurs, as hypotonic fluids may be required. Among the patients that experienced an over-rapid increase in sNa in 24 hours (≥12 mmol/L), 7 patients received oral or intravenous hypotonic fluids, while 10 patients did not receive any additional treatment and sNa was monitored without further documented complications.

Kinugawa K et al (2019)[18]

SMILE Study

In Japan, tolvaptan is indicated for patients with heart failure and volume overload who have inadequate response to other diuretics. In contrast to the USA and Europe, tolvaptan can be used in Japan in patients with normal sodium levels.

In this multi-centre, non-interventional, post-marketing surveillance study, prospective data from 3,349 patients treated with tolvaptan over a 5-year period were analysed to identify benefits and risks.

The overall incidence of ADRs was 18.1%. The most common ADR was thirst (8.4%), followed by hypernatremia (4.4%). Of reported cases of hypernatremia, 0.4% were assessed as serious by the attending physicians. No case of central pontine myelinolysis (CPM) was reported. Rapid correction of serum sodium concentration, defined as a 12mEq/L increase within 24h, was reported for 8 (0.2%) patients. Serious renal dysfunctional was reported for 11 patients, all of whom had renal dysfunction caused by loop diuretics or worsening HF as a complication before the start of tolvaptan treatment. Serious hepatic dysfunction was reported for 6 patients, of which 4 cases were considered to be related to tolvaptan treatment; 2 of the 6 patients died (liver failure; disseminated intravascular coagulation) and the remaining 4 patients recovered with or without a dose reduction or discontinuation of tolvaptan.

ADRs were most frequent in the group treated with tolvaptan 15mg. This group also had the highest incidence of thirst and hypernatremia. Dose proportionality was not observed for renal or hepatic dysfunction.

Incidence of Physician-Reported Adverse Drug Reactions According to Tolvaptan Dose				
Parameter	3.75 mg	7.5 mg	15 mg	P value[a]
Adverse drug reaction	12.6 (40/317)	15.4 (271/1,760)	18.1 (140/772)	0.0162
Thirst	5.1	6.8	9.2	0.0080
Hypernatremia	2.8	3.7	6.4	0.0017
Renal dysfunction[b]	1.0	1.0	1.2	0.7366
Hepatic dysfunction[c]	1.3	0.8	0.7	0.5820

Berl et al. (2010)15

SALTWATER trial

SALTWATER was a multi-centre, open-label extension of the Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and SALT-2). In total, 111 patients with hyponatremia received oral tolvaptan for a mean follow-up of 701 days, providing 77,369 patient-days of exposure. All patients had hyponatremia at randomisation in SALT-1 and SALT-2, and 85% continued to have hyponatremia at entry in SALTWATER.

AEs that occurred in >10% of patients (drug-related or -unrelated) included peripheral oedema (25 patients), hyponatremia (23 patients), anaemia (20 patients), diarrhoea (19 patients), urinary tract infection (18 patients), nausea (17 patients), fatigue (15 patients), hypokalaemia (14 patients), headache (14 patients), ascites (13 patients), hypotension (13 patients), pneumonia (13 patients), cardiac failure (12 patients), thirst (12 patients), and dizziness (12 patients). Among the 23 patients with reports of hyponatremia, 11 experienced their episodes during the treatment period (three during interruptions in tolvaptan therapy) and 13 during the post treatment period. The most common AEs assessed by the investigator as being potentially related to tolvaptan use were pollakiuria (11 patients); thirst (10 patients); fatigue (six patients); and dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral oedema, and acute renal failure.

Of the 64 patients who withdrew from the study during the 214-week treatment period, 19 withdrew for a treatment emergent AE of any cause. The AEs in six of these 19 patients subsequently resulted in death (cardiac failure [two patients], oesophageal varices, hepatic cirrhosis, cerebral haemorrhage, and gastrointestinal haemorrhage). The AEs in the remaining 13 patients led to discontinuation but not death (ventricular tachycardia, vertigo, gastrointestinal haemorrhage, vomiting, gait disturbance, irritability, serum creatinine increase, serum sodium increase, anorexia, bladder cancer, dysphasia, myocardial infarction, psychotic disorder, renal failure, and pruritus). An additional 13 patients died as an outcome of an AE without being withdrawn from the study as a result of the event (cardiac failure [three patients], renal failure [two patients], hepatorenal syndrome, cardiorespiratory arrest, cardiac arrest, pneumonia, cerebral haemorrhage, respiratory failure, sepsis, and urosepsis).

Six AEs leading to drug discontinuation were assessed by the investigator as possibly or probably related to tolvaptan therapy and included severe ventricular tachycardia (on day 3), severe irritability (day 14), mild serum sodium increase (day 15), mild anorexia (day 22), severe serum creatinine increase (day 329), and moderate pruritus (day 513). Ten patients experienced at least one serious AE assessed by the investigator as potentially related to study treatment. The events were not adjudicated by a review committee and are presented as described by the investigator. Of the 19 patients who died during the study, one case of severe hepatorenal syndrome resulting in death occurred in a 65-year-old woman on day 53 and was judged by the investigator to be possibly related to study medication use.

Summary of Product Characteristics1

Special populations

- *Renal impairment*

  Tolvaptan is contraindicated in anuric patients.

  Tolvaptan has not been studied in patients with severe renal failure. The efficacy and safety in this population is not well established.

  Based on the data available, no dose adjustment is required in those with mild to moderate renal impairment.

- *Hepatic impairment*

No information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing has to be managed cautiously and electrolytes and volume status must be monitored. No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Contraindications

- Hypersensitivity to the active substance or to any of the excipients or to benzazepine or benzazepine derivatives
- Anuria
- Volume depletion
- Hypovolemic hyponatremia
- Hypernatremia
- Patients who cannot perceive thirst
- Pregnancy - Women of childbearing potential must use effective contraception during tolvaptan treatment
- Breast-feeding

Special warnings and precautions for use

- Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely. For such patients, alternative treatment must be considered.
- Tolvaptan may cause adverse reactions related to water loss such as thirst, dry mouth and dehydration. Therefore, patients must have access to water and be able to drink sufficient amounts of water. If fluid restricted patients are treated with tolvaptan, extra caution has to be exercised to ensure that patients do not become overly dehydrated.
- Volume status must be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake.
- Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.
- Fluid and electrolyte status has to be monitored in all patients and particularly in those with renal and hepatic impairment. Administration of tolvaptan may cause too rapid increases in serum sodium (≥ 12 mmol/L per 24 hours); therefore, monitoring of serum sodium in all patients must start no later than 4-6 hours after treatment initiation. During the first 1-2 days and until the tolvaptan dose is stabilised serum sodium and volume status must be monitored at least every 6 hours.
- Patients with very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium.
  Too rapid correction of hyponatremia (increase ≥ 12 mmol/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. Therefore, after initiation of treatment, patients have to be closely monitored for serum sodium and volume status.

  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.

  Patients who received other treatment for hyponatremia or medicinal products which increase serum sodium concentration prior to initiation of treatment with Samsca must be managed very cautiously. 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.

  Co-administration of Samsca with other treatments for hyponatremia, and medicinal products that increase serum sodium concentration, is not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations.

- Diabetic patients with an elevated glucose concentration (e.g. in excess of 300 mg/dL) may present with pseudo-hyponatremia. This condition should be excluded prior and during treatment with tolvaptan.

  Tolvaptan may cause hyperglycemia. Therefore, diabetic patients treated with tolvaptan should be

managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.

- Liver injury induced by tolvaptan was observed in clinical trials investigating a different indication (autosomal dominant polycystic kidney disease [ADPKD]) with long-term use of tolvaptan at higher doses than for the approved indication.

  In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.

  Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after discontinuation of tolvaptan. These findings may suggest that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

  Liver function tests must be promptly performed in patients taking tolvaptan who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If liver injury is suspected, tolvaptan must be promptly discontinued, appropriate treatment has to be instituted, and investigations have to be performed to determine the probable cause. Tolvaptan must not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

- In post-marketing experience, anaphylaxis (including anaphylactic shock and generalised rash) has been reported very rarely following administration of tolvaptan. Patients have to be carefully monitored during treatment. Patients with known hypersensitivity reactions to benzazepine or benzazepine derivatives (e.g. benazepril, conivaptan, fenoldopam mesylate or mirtazapine) may be at risk for hypersensitivity reaction to tolvaptan.
- Samsca contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interaction with other medicinal products and other forms of interaction

- Concomitant use of Samsca with other treatments for hyponatremia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium and is therefore not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations where rapid correction may represent a risk for osmotic demyelination.

- Tolvaptan plasma concentrations have been increased by up to 5.4-fold area under time-concentration curve (AUC) after the administration of strong CYP3A4 inhibitors. Co-administration of grapefruit juice and tolvaptan resulted in a 1.8-fold increase in exposure to tolvaptan. Patients taking tolvaptan should avoid ingesting grapefruit juice.

- Tolvaptan plasma concentrations have been decreased by up to 87 % (AUC) after the administration of CYP3A4 inducers. Caution has to be exercised in co-administering CYP3A4 inducers (e.g. rifampicin, barbiturates) with tolvaptan.

- While there does not appear to be a synergistic or additive effect of concomitant use of tolvaptan with loop and thiazide diuretics, each class of agent has the potential to lead to severe dehydration, which constitutes a risk factor for renal dysfunction.

- Steady state digoxin concentrations have been increased (1.3-fold increase in maximum observed plasma concentration [C_{max}] and 1.2-fold increase in area under the plasma concentration-time curve over the dosing interval [AUC_{τ}]) when co administered with multiple once daily 60 mg doses of tolvaptan.

- In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V2-receptors involved in the release of coagulation factors (e.g., von Willebrand factor) from endothelial cells. Therefore, the effect of vasopressin analogues such as desmopressin may be attenuated in patients using such analogues to prevent or control bleeding when co-administered with tolvaptan.

Undesirable effects

The pharmaco-dynamically predictable and most commonly reported adverse reactions are thirst, dry mouth and pollakiuria occurring in approximately 18 %, 9 % and 6 % of patients.

System Organ Class	Frequency			
	Very common	Common	Uncommon	Not known
Immune system disorders				Anaphylactic shock, Generalised rash
Metabolism and nutrition disorders		Polydipsia, Dehydration, Hyperkalemia, Hyperglycemia, Hypoglycemia[1], Hypernatremia[1], Hyperuricemia[1], Decreased appetite		
Nervous system disorders		Syncope[1], Headache[1], Dizziness[1]	Dysgeusia	
Vascular disorders		Orthostatic hypotension		
Gastrointestinal disorders	Nausea	Constipation, Diarrhoea[1], Dry mouth		
Skin and subcutaneous tissue disorders		Ecchymosis, Pruritus	Pruritic rash[1]	
Renal and urinary disorders		Pollakiuria, Polyuria	Renal impairment	
General disorders and administration site conditions	Thirst	Asthenia, Pyrexia, Malaise[1]		
Hepatobiliary disorders				Hepatic disorders[2] Acute hepatic failure[3]
Investigations		Blood urine present[1], Alanine aminotransferase increased[1], Aspartate aminotransferase increased[1], Blood creatinine increased	Bilirubin increased[1]	Elevated transaminases[2]
Surgical and medical procedures	Rapid correction of hyponatremia, sometimes leading to neurological symptoms			

[1] observed in clinical trials investigating other indications

[2] from post-authorisation safety study in hyponatremia secondary to SIADH

[3] observed in post-marketing with tolvaptan in ADPKD. Liver transplantation was necessary.

Strengths and limitations of the evidence:

Strengths

- Tolvaptan has been studied for nearly 30 years
- Two large multi-centre, randomised, double-blind, placebo-controlled, efficacy and safety studies of the effects of titrated oral tolvaptan tablets in patients with hyponatremia have been conducted
- There is evidence of an effect on the serum sodium levels and the secondary parameters including urine output, fluid intake and overall fluid balance
- Vasopressin receptor antagonists may reduce the length of hospital stay in some patients

Limitations

- In the main two studies, there were a mixture of aetiologies causing the hyponatraemia
- The main studies compare tolvaptan to placebo; data for other interventions to correct hyponatremia is lacking
- Trial duration of the 2 main studies was only 30 days, so it is difficult to ascertain the effects on serum sodium beyond the treatment phase and incidence of side effects with extended use
- Continued tolvaptan therapy may be needed to maintain serum sodium normalisation
- There is some evidence to suggest that a lower starting dose of 7.5mg may be more appropriate to reduce the risk of over correction of hyponatraemia
- According to a Cochrane analysis, vasopressin receptor antagonists have uncertain effects on death at six months and the potential for liver toxicity remains uncertain

Summary of evidence on cost effectiveness:

Drug costs

Tolvaptan (Samsca) 7.5mg = £448.08 for 10 tablets (drug tariff Nov 2022)

15mg = £746.80 for 10 tablets (NHS dm+d browser)

30mg = £746.80 for 10 tablets (NHS indicative price, BNF)

Initiate at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily.

Cost per dose approx. £45 - £150.

Demeclocycline 150mg = £238.41 for 28 capsules (drug tariff Dec 2022)

Initially 0.9–1.2 g daily in divided doses, maintenance 600–900 mg daily.

Cost per day approx. £34 - £68

Duration of both treatments is dependent on length of time to normalisation of sodium levels and maintenance of normalisation. Duration of treatment with tolvaptan may be limited to a maximum of 30 days due to the incidence of side effects and monitoring requirements.

CADTH (2013)[9]

The Canadian Drug Expert Committee (CDEC) recommends that tolvaptan not be listed. Tovalptan was not considered to be cost-effective in patients with heart failure and non-hypovolemic hyponatremia and there was insufficient pharmacoeconomic evidence to evaluate the use of tolvaptan for the treatment of non-hypovolemic hyponatremia in other patient populations.

Jamookeeah et al (2016)[19]

We investigated the cost-effectiveness of tolvaptan versus no active treatment (NAT) in adult patients within the licensed indication who have either failed to respond to fluid restriction or for whom the use of fluid restriction is not suitable, from the societal perspective in Sweden.

A cost-utility analysis, considering a 'general SIADH' population and two subpopulations of patients (small-cell lung cancer [SCLC] and pneumonia) to broadly represent the complex clinical pathway of SIADH, was

performed. Clinical data were derived from tolvaptan trials and observational data sources. All costs are given in Swedish kronor (SEK).

In the 'general SIADH' population, tolvaptan was associated with reduced costs (SEK 5,779 per patient [€624]) and increased quality-adjusted life-years (QALYs) (0.0019) compared with NAT and was therefore the dominant treatment strategy. Tolvaptan was also associated with reduced costs and increased QALYs in the SCLC and pneumonia subpopulations. The most influential variables in our analysis were reduction in hospital length of stay, duration of treatment and long-term treatment with tolvaptan in SCLC patients. Tolvaptan represents a cost-effective treatment option in Sweden for hospitalised patients with HN secondary to SIADH who have either failed to respond to or are unsuitable for fluid restriction.

Prescribing and risk management issues:

- Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, treatment with Samsca must be initiated in hospital.
- For patients at risk of overly rapid correction of sodium e.g. patients with oncological conditions, very low baseline serum sodium, taking diuretics, or taking sodium supplementation, a dose of 7.5 mg should be considered.
- Several brands of tolvaptan are available; prescribers should take care to select the relevant product for the indication.
- The FDA recommend that tolvaptan should not be used for more than 30 days due to reports of potentially fatal liver injury in patients with autosomal dominant polycystic kidney disease.
- Patients must have access to water and be able to drink sufficient amounts of water.
- Patients taking tolvaptan should avoid ingesting grapefruit juice.

Commissioning considerations:

Innovation, need and equity implications of the intervention:

None identified

Financial implications of the intervention:

Tolvaptan (Samsca) daily drug cost approx. £45 - £150

Demeclocycline daily drug cost approx. £34 - £68

Additional costs During the first 1-2 days and until the tolvaptan dose is stabilised serum sodium and volume status must be monitored at least every 6 hours.

It is anticipated that the **number** of patients being treated for hyponatraemia secondary to SIADH, where fluid restriction has been unsuccessful or is inappropriate, will remain unchanged. The potential additional cost would be those treated with tolvaptan rather than demeclocycline. The magnitude of the cost impact is highly dependent on the maintenance dose of either drug and the duration of treatment.

Service Impact Issues Identified:

None identified

Equality and Inclusion Issues Identified:

None identified

Cross Border Issues Identified:

The **Pan Mersey APC** recommends the prescribing of tolvaptan tablets (Samsca), by specialists only, for the treatment of hyponatraemia secondary to SIADH due to any cause.

RAG rating RED.

Tolvaptan should only be initiated by a consultant endocrinologist.

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

The **Greater Manchester Medicines Management Group** (GMMMG) recommends tolvaptan for SIADH.

RAG rating RED.

Legal Issues Identified:

None identified

Media/ Public Interest:

None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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