Summary

The drug and the review
- Tolvaptan is an oral selective vasopressin V2 receptor antagonist, which blocks the binding of arginine vasopressin in the kidneys and induces free water clearance without depleting electrolytes (aquaresis).
- Tolvaptan was licensed for the treatment of hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion in adults in the UK in August 2009.
- This review evaluates the evidence for the use of tolvaptan in the licensed indication and seeks to define its place in therapy.

Background
- Dilutional hyponatraemia is defined as a greater amount of water to sodium in the plasma; this is in contrast to depletional hyponatraemia where there is a total reduction in the amount of sodium in the plasma. Hyponatraemia (plasma sodium <135mmol/L) is common in acutely ill patients and occurs in ~15-30% of hospitalised patients.
- In hypovolaemic hyponatraemia, both total body water and sodium are decreased, with a greater decrease in sodium.
- In euvolaemic hyponatraemia there is an increase in total body water and near normal total body sodium.
- In hypervolaemic hyponatraemia, both total body sodium and water are increased, but with the greater increase being in total body water.
- Not all types of hyponatraemia can be treated with isotonic saline administration, some require restricted fluid intake, and if this is not tolerated or not complied with, treatments such as demeclocycline can be used (unlicensed treatment indication).

Literature
- We searched the following databases for studies assessing the efficacy and safety of tolvaptan for hyponatraemia, and for health economic assessments: Embase, Medline, IDIS.
- Two pivotal, phase 3, randomised, double-blind, placebo-controlled trials were identified (SALT-1 and -2), which were reported together. One smaller open-label study was identified.
- The manufacturers, Otsuka Pharmaceuticals (UK) Ltd, were contacted.
**Efficacy studies**

- The Study of Ascending Levels of Tolvaptan in hyponatraemia (SALT-1 and -2) studies were of identical design and assessed the efficacy of tolvaptan in patients with non-acute euvoalaemic or hypervolaemic hyponatraemia.
  - Patients had a variety of underlying conditions including concurrent chronic heart failure, liver cirrhosis or syndrome of inappropriate antidiuretic hormone (SIADH) and treatment was stratified according to whether their hyponatraemia was marked (<130mmol/L) or mild (130-134mmol/L).
  - Treatment was allocated in a 1:1 ratio: tolvaptan 15-60mg (n=225) or placebo (n=223) and was given for up to 30 days, the first day of which was spent in hospital. Doses were increased over the first 4 days according to a set regimen for slow sodium correction. Fluid restriction was not mandatory and was to be avoided in the first 24h. Demeclocyline, lithium chloride or urea were not permitted for the treatment of hyponatraemia.
  - The primary endpoints were the change in the average daily area under the curve (AUC) for the serum sodium concentrations (mmol/L) from baseline to day 4 and from baseline to day 30. Changes in the tolvaptan groups were significantly greater than in the placebo groups at both time points:
    - Day 4: 3.62 vs. 0.25mmol/L (tolvaptan vs. placebo, SALT-1) and 4.33 vs. 0.42mmol/L (tolvaptan vs. placebo, SALT-2) (p<0.001 for both studies favouring tolvaptan).
    - Day 30: 6.22 vs. 1.66mmol/L (tolvaptan vs. placebo SALT-1) and 6.20 vs.1.84mmol/L (tolvaptan vs. placebo, SALT-2) (p<0.001 for both studies favouring tolvaptan).
  - Tolvaptan therapy was significantly better than placebo for these secondary endpoints:
    - Change in AUC at days 4 and 30 for patients with marked hyponatraemia (n<0.001 for both studies)
    - Absolute serum sodium concentrations at each visit (p<0.001, for both studies) and time to normalisation of serum sodium concentration (no data shown). A significant difference was seen as early as within 8 hours of the first drug administration.
    - Percentages of patients with normalised serum sodium concentration and the categorisation of serum sodium concentration at days 4 and 30 (p<0.001 for both studies)
    - Fluid intake and output on day 1 (p<0.001 for both studies).
  - Subgroup analysis of patients with SIADH showed that tolvaptan was significantly more efficacious than placebo in raising serum sodium. Differences between the treatment were lost soon after tolvaptan was discontinued (day 37).
  - The SALT studies show that tolvaptan does correct hyponatraemia in this patient population when used for a month. After therapy had stopped, the serum sodium concentrations achieved with tolvaptan fell to those associated with placebo use.

- The primary objective of the open label study was to assess the effect of tolvaptan vs. fluid restriction on serum sodium concentration.
  - Patients were randomised 2:1 to tolvaptan (n=15) or fluid restriction (<1200mL/day) (n=8) for up to 27 days. Fluid restriction was individualised to achieve serum sodium concentrations within normal limits. Only six patients randomised to tolvaptan and two randomised to placebo completed the entire 28 days.
  - Significantly larger increases in serum sodium concentrations were seen with tolvaptan than with fluid restriction (p=0.0065). Normalisation of serum sodium concentrations were achieved more rapidly in the tolvaptan group: 50% by day 4 compared with day 8 in the fluid restricted group (p<0.03).

**Safety**

- The most common side effects seen with tolvaptan were thirst and dry mouth.
- In the SALT studies, eight serious adverse events leading to study withdrawal occurred in the tolvaptan group, including rash / exanthema, nocturia, urinary frequency, muscle weakness and hypernatraemia. Eight also occurred in the placebo group, leading to study withdrawal (including acute renal failure in 2 patients, rash in 2 patient, dysgeusia (altered taste), decrease serum sodium concentrations, increased serum creatinine).
Critical evaluation

- There are a number of limitations to the SALT-1 and -2 studies:
  - Patients with hyponatraemia due to transient causes were excluded from the study. Unless the underlying cause of hyponatraemia is resolved it would be anticipated that, without treatment, hyponatraemia would persist.
  - Post-hoc subgroup analysis of patients with SIADH has only been published as a conference abstract. Although p values show statistical significance in favour of tolvaptan, few figures are given so the data is hard to fully interpret.
  - The groups were well matched at baseline with regards to percentages of patients enrolled with chronic heart failure, liver cirrhosis and SIADH. However, no sub-group analyses were carried out for each of the patient groups enrolled so it is unknown whether tolvaptan is equally as effective in each group.
  - There was no indication of how hyponatraemia was treated in the placebo group and whether this treatment was appropriate. As already mentioned, fluid restriction was not mandatory (it was at the discretion of the investigator) and the use of demeclocyline, lithium chloride and urea, which are used to treat hyponatraemia, was not allowed. Fluid restriction is generally the accepted standard of care of non-acute euvoalaemic and hypervolaemic hyponatraemia. These drug treatments are usually reserved for patients where fluid restriction alone is not sufficient.
  - Patients with severe <120mmol/L, symptomatic HN were excluded and therefore data is lacking in this sub-population.
  - There was no mandated fluid restriction or change in patient’s medication, including those using diuretics which are more likely to be used in patients with chronic heart failure (CHF) or cirrhosis. The data from patients taking diuretics was not analysed separately. Tolvaptan is not licensed for use in CHF.
  - Almost a quarter of patients taking tolvaptan and third of patients taking placebo withdrew from the studies; no details are given and no comment is made on this apart from the small number who withdrew due to adverse events.
  - Open label phase II study
    - The study population was very small as it was a 'proof of concept' phase II study: 28 patients were enrolled rather than the planned 78, but the authors stated this was enough to power the study.
    - The study design required patients to return for frequent outpatient visits and may have affected compliance. Only 8 patients completed the study.
    - The cause of hyponatraemia varied among patients and evaluating the response by cause was not possible due to the small numbers.

Potential benefits over existing technologies

- Tolvaptan will be the first licensed medication for the treatment of hyponatraemia secondary to SIADH in the UK.
- Hyponatraemia is corrected more quickly with tolvaptan therapy than with fluid restriction, though the effects diminish once tolvaptan is discontinued unless the underlying cause of hyponatraemia has been resolved. Treatment with tolvaptan should be interrupted at intervals in order to reassess the need for continued treatment.

Potential disadvantages over existing technologies

- There are a number of limitations to the pivotal SALT studies. The effects of tolvaptan in a wider range of patients can only be assessed once it is used in clinical practice.
- Tolvaptan requires initiation in hospital due to monitoring requirements and possible dose titration.
- It is yet to be seen whether tolvaptan improves the overall prognosis.
Health Economics
• No analyses have been identified.

Estimated cost per 100 000 population

It is anticipated by Otsuka Pharmaceuticals that tolvaptan will be initiated and used by secondary care clinicians. Otsuka have supplied a budgetary impact model.

Tolvaptan is supplied in packs of 10x 15mg or 30mg tablets; each 15mg or 30mg tablet costs £74.68. Dosing starts at 15mg/day and can be increased to a maximum of 60mg/day to achieve the desired serum sodium level.

The estimated budget impact of introducing tolvaptan is based on the following:
• 4 patients undergoing treatment with tolvaptan for their initial period of in-patient care
• The conservative treatment cost per patient of £866.29 is used, based on length of inpatient stay, titration phase and drug costs.

An additional £3,465.16 would be spent on the prescription of tolvaptan per 100,000 patients per year. This is associated with a potential cost offset of £4,106.39 in reduction in in-patient costs.

The economic model presented by Otsuka Pharmaceuticals does not take into account continued out-patient treatment.

Issues for consideration
• It is unclear whether the use of tolvaptan will just treat the symptoms of hyponatraemia or actually improve the outcome of the associated medical conditions.
• The symptoms of chronic hyponatraemia, as studied in the SALT trials, are subtle and include cognitive impairment. The data regarding improvements in the mental component summary score of the SF-12 health survey questionnaire indicated statistically significant improvements in mental function.
• In the SALT trials, when tolvaptan use is stopped, sodium levels returned to those seen with placebo treatment (within ~ 1 week of discontinuation). Patients with transient causes of HN were excluded from the SALT trials and it anticipated that unless the underlying cause of hyponatraemia has been resolved for example, non-small cell lung cancer or pneumonia, treatment with tolvaptan should be interrupted at intervals in order to reassess the need for continuation, as per the SmPC.
Background

Tolvaptan was launched in the EU for the treatment of adult patients with hyponatraemia, secondary to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, in August 2009. Tolvaptan is a vaso-pressin antagonist which blocks the binding of arginine vasopressin at the V2 receptors of the distal portions of the nephron, resulting in free water clearance (aquaresis) without depletion of electrolytes. Treatment should be initiated in hospital, due to the close monitoring of serum sodium and volume status that is required.

Hyponatraemia

Hyponatraemia indicates a greater amount of water to sodium in the plasma and is defined as a serum sodium concentration of <135mmol/L. Hyponatraemia is common in acutely ill patients and occurs in approximately 15-30% of hospitalised patients. It is associated with a range of disorders, such as chronic heart failure, liver cirrhosis and syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Clinical features include lethargy and anorexia, leading to disorientation, seizures and coma. An acute onset may cause cerebral oedema.

Hyponatraemia is classified according to water and sodium loss:

- In hypovolaemic hyponatraemia there is a decrease in both total body water and sodium but relatively less deficit of water.
- Euvolaemic hyponatraemia indicates an increase in total body water and near normal total body sodium. There is no evidence of extracellular fluid volume (ECFV) depletion or excess, i.e. no peripheral oedema, ascities, pulmonary congestion or pleural effusions. Hypothyroidism, hypopituitarism, severe emotional (e.g. psychosis) or physical stress and various medications that stimulate antidiuretic hormone should be ruled out before SIADH is diagnosed.
- In hypervolaemic hyponatraemia, both total body sodium concentration and water are increased, but total body water is increased more, resulting in hyponatraemia. Decreased plasma sodium concentration is a risk factor for poor survival in patients with cardiac failure or cirrhosis.

The diagnosis of SIADH requires concentrated urine (sodium >20mmol/L and osmolality >500mosmol/kg) and hyponatraemia (<135mmol/L) or low plasma osmolality and the absence of hypovolaemia, oedema or diuretics. The antidiuretic hormone involved is arginine vasopressin (AVP). There are many causes of SIADH, such as malignant disease, pulmonary disorders and central nervous system disorders, as well as a number of drugs which stimulate the release of AVP or enhance its action, such as SSRI antidepressants, carbamazepine, vincristine. Other drugs, such as desmopressin and oxytocin are AVP analogues and are causes of SIADH.

The only definitive treatment of SIADH is elimination of its underlying cause. The correct treatment of hyponatraemia depends upon the correct diagnosis:

- In hypovolaemic hyponatraemia, volume expansion with isotonic saline should be tried.
- In asymptomatic patients with chronic euvolaemic or hypervolaemic hyponatraemia in which no specific intervention is available, fluid restriction is generally the treatment of choice. The daily fluid intake must be less than the 24 hour urine output + insensible losses; e.g. for a daily urine output of 500mLs and average daily insensible losses of 250mL, the total daily intake must be less than 750mLs to create a negative water balance and increase serum sodium concentrations. If this is not tolerated or complied with, the drug treatment can be used.
- Demeclocycline induces nephrogenic diabetes insipidus and has been used to treat chronic hyponatraemia. It is liver metabolised and nephrotoxicity has been reported in patients with liver disease and with congestive heart failure.
- Oral urea has been used but is unpalatable and needs to be taken with orange juice or similar to improve the taste.
- Lithium can cause nephrogenic diabetes insipidus and is therefore not recommended to treat hyponatraemia. These three drugs do not have a UK licence for the treatment of hyponatraemia.
Tolvaptan

Stimulation of V2 receptors by AVP leads to an antidiuretic effect and increases free water reabsorption, resulting in tissue oedema and dilution of sodium concentrations to produce hyponatraemia.6 The cardiovascular effects of AVP are predominantly caused by stimulation of V1a receptors, causing peripheral and coronary vasoconstriction (see figure 1, page 7). Tolvaptan is 29 times more selective for V2 than V1a receptors and produces significant aquaresis (water diuresis without electrolyte excretion) and increases serum sodium.6

Dose

The recommended dose is 15mg once a day, which can be increased to a maximum of 60mg daily as tolerated, to achieve the desired serum sodium level.1 The treatment duration is determined by the underlying disease and its treatment. However, treatment with tolvaptan is expected to last until the underlying disease is adequately treated or until such time that hyponatraemia is no longer a clinical issue.

Pharmacokinetics

After oral administration tolvaptan is rapidly absorbed with the maximum concentration being reached after 2-3 hours. The Cmax is higher in patients with heart failure, who have an increased extra-cellular volume. Tolvaptan has a half life of 6-8 hours.7

Metabolism of tolvaptan is primarily through the CYP3A4 enzyme system, making it susceptible to drug interactions.6

Special populations

The use of tolvaptan in pregnancy is contraindicated because of teratogenicity seen in animal studies.2

Clinical efficacy: SALT-1 and -2

The two Study of Ascending levels of Tolvaptan in hyponatraemia (SALT 1 and 2) trials have assessed the efficacy of tolvaptan in patients with euvoalaemic or hypervolaemic hyponatraemia.8 Both studies were identical, randomised, double-blind, placebo-controlled, phase 3 trials and assessed the outpatient use of tolvaptan. These were the pivotal studies submitted for licensing. SALT-1 was carried out in the US and SALT-2 in the US, Canada and EU.9

Patients aged 18 years or older, with chronic heart failure, liver cirrhosis or SIADH in association with hyponatraemia were enrolled. No one single disease could make up more than 50% of the total study population and a serum sodium concentration of <130mmol/L at baseline (marked hyponatraemia) was required in 50% of the study population. There were a number of exclusion criteria, including hypovolaemic hyponatraemia, in which normal plasma sodium concentration could be re-established by restoring plasma volume, myocardial infarction, severe angina, cerebrovascular accident, systolic blood pressure <90mm Hg or a Child-Pugh score >10.

Patients were stratified according to whether their hyponatraemia was mild (130-134 mmol/L of sodium) or marked (<130 mmol/L), and whether or not it was associated with chronic heart failure. Treatment was assigned in a 1:1 ratio for either tolvaptan (15mg tablet) or matching placebo for up to 30 days, which was added to the patient’s standard therapy. (see table 1). Fluid restriction was not mandatory. Demeclocyline, lithium chloride or urea were not permitted for the treatment of hyponatraemia. The tolvaptan dose could be increased from 15mg to 30mg, or from 30mg to 60mg, during the first 4 days of therapy, according to a set regimen designed for slow correction of serum sodium concentration. The dose was increased if the serum sodium remained <136mmol/L and had increased by <5mmol/L during the prior 24 hours. If the serum sodium rose >145mmol/L or increased at more than 12mmol/L/24 hours or >8mmol/L/8 hours on the first day, the dose was either withheld or the fluid intake increased. Patients were hospitalised for the first day of the study but the majority were discharged by day 4. The effects of discontinuing the drug at day 30 were assessed on day 37.

A sample of 100 patients per group were required to give the study 90% power to detect a mean between-group difference of 1.99±2.7 mmol sodium/L in the change from baseline to day 4 and 3.00±3.28 mmol sodium/L from baseline to day 30.
The studies had two primary endpoints, namely the change in the average daily area under the curve (AUC) for the serum sodium concentration from baseline to day 4 and from baseline to day 30. In both studies, changes at days 4 and through to day 30 were significantly greater in the tolvaptan group compared to the placebo group (p<0.001). Tolvaptan therapy also provided a significantly greater increase in the average daily AUC, stratified according to whether baseline hyponatraemia was mild or marked (see Table 2, page 8 for results). Within 8 hours of the first administration the serum sodium concentrations were significantly higher in the tolvaptan group than in the placebo group for both the overall population and the subgroups stratified according to the degree of hyponatraemia. This was maintained throughout the study.

There were a number of secondary endpoints (see Table 2, for results):

- Change in the AUC for the serum sodium concentration in patients with marked hyponatraemia. At day 4 and through to day 30, the change in AUC was significantly greater with tolvapatan therapy than with placebo (p<0.001 for each study).
- Absolute serum sodium concentration at each visit. The mean concentrations were significantly greater in the tolvaptan than in the placebo group at both visits (p<0.001 for each study).
- The time to normalization of the serum sodium concentration. The serum sodium concentration approached the normal range more rapidly in the tolvaptan group than in
The percentages of patients with serum sodium concentrations that had normalised at day 4 and day 30. Significantly more patients in the tolvaptan group than in the placebo group had normalised serum sodium concentrations by day 4 and by day 30 (p<0.001 for both days, for each study).

Categorical serum sodium concentration on day 4 and day 30 for patients with mild or marked hyponatremia at baseline, i.e. marked, mild or normal hyponatraemia. Significantly fewer patients in the tolvaptan group were classified as having marked hyponatraemia at days 4 and 30, compared to the placebo group.

Fluid intake and output on day 1. The difference between fluid intake and urine production during the first day was significantly greater in the tolvaptan group than in the placebo group (p<0.001 for each study). There was a trend towards fewer patients requiring fluid restriction in the tolvaptan group (p=0.08 for each study).

Change from baseline in scores on the Physical Component Summary and Mental Component Summary of the Medical Outcomes Study 12-item Short-Form (SF-12) General Health Survey (ranges 5-69 for the physical and 8-73 for the mental components, higher scores indicating better function). Scores for the Physical Component Summary (including physical functioning, bodily pain, general health) did not differ significantly between the groups. Those for the Mental Component Summary (including vitality, social functioning, calmness) improved in the combined analysis (p=0.02) and in SALT-1 (p=0.04) but not in SALT-2 (p=0.14). Scores for the Mental Component improved significantly in patients with marked hyponatraemia (p=0.04).

Results of two other specified secondary endpoints were not published: Change in body weight in patients with hypervolemic hyponatremia on day 1 and use of intravenous saline as rescue therapy.

Subgroup analysis was performed on patients who had SIADH (tolvaptan n=86, placebo n=90, no treatment n=3). Data comes from a conference abstract: p values were stated for each assessment but few figures were given, making the data difficult to fully interpret. Tolvaptan was superior to placebo.

Table 1: Patient characteristics and treatment assignment

<table>
<thead>
<tr>
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<th>SALT 1</th>
<th>SALT 2</th>
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<tbody>
<tr>
<td></td>
<td>Tolvaptan (n=102)</td>
<td>Placebo (n=103)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>35 (34%)</td>
<td>33 (32%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>25 (25%)</td>
<td>21 (20%)</td>
</tr>
<tr>
<td>SIADH and other cause</td>
<td>42 (41%)</td>
<td>49 (48%)</td>
</tr>
<tr>
<td>Mild hyponatraemia Mean serum sodium mmol/L</td>
<td>49 (48%)</td>
<td>132.4±1.5</td>
</tr>
<tr>
<td>Marked hyponatraemia Mean serum sodium mmol/L</td>
<td>53 (52%)</td>
<td>125.4±3.5</td>
</tr>
<tr>
<td>Randomised</td>
<td>102</td>
<td>103</td>
</tr>
<tr>
<td>Included in safety analysis</td>
<td>100</td>
<td>101</td>
</tr>
<tr>
<td>Included in efficacy analysis</td>
<td>95</td>
<td>89</td>
</tr>
<tr>
<td>Completed 30 day study period and 7 day follow up</td>
<td>79 (77.5%)</td>
<td>65 (63.1%)</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>23 (22.5%)</td>
<td>38 (36.9%)</td>
</tr>
</tbody>
</table>
for:

- Change in average daily AUC for serum sodium concentration between baseline to day 4 and day 30
  \( (p<0.001) \)
- Mean serum sodium changes at each time point. The maximal mean serum sodium change from baseline on day 30 was 8.5mEq/L (tolvaptan) and 2.9 mEq/L (placebo), \( (p<0.001) \)
- Time to normal serum sodium
  \( (p<0.001) \)
- Percent of patients with normal serum sodium levels at days 4 and 30
  \( (p<0.001) \)

Fewer patients receiving tolvaptan (5%) required fluid restriction compared with placebo (22%, \( p=0.001 \)). Differences between the tolvaptan and placebo groups were lost after stopping tolvaptan (by day 37).

During the follow-up week after discontinuation, there were no differences in the decline in serum sodium concentrations between the SALT 1 and 2. Serum sodium concentrations achieved with tolvaptan fell to those associated with placebo use, indicating that continued use of tolvaptan was required to maintain normal sodium concentrations.

A similar percentage of patients suffered adverse events in both groups. In total, there were 26 serious adverse events possibly related to study treatment, (11 in tolvaptan and 15 in placebo groups). Eight serious adverse events leading to study withdrawal were due to tolvaptan, and included: rash, nocturia, urinary frequency, exanthema, muscle weakness and hypernatraemia. There were also eight adverse events leading to withdrawal in the placebo group: acute renal failure (2 patients), rash (2 patients), dysgeusia (altered taste), decreased serum sodium concentrations, vomiting, aggravated hyponatraemia, and increased serum creatinine. The most common side effects that occurred with tolvaptan were thirst and dry mouth, seen in 14% and 13% of patients in SALT-1 and 5% and 4% in SALT-2 respectively.

In four patients out of 223 in the tolvaptan group, the desirable rate of sodium correction was exceeded during the first 24 hours (>0.5mmol/L/hr, the maximum seen was 0.61mmol/L/hr). The serum sodium concentration rose above 145mmol/L in four patients taking tolvaptan.

The SALT-1 and SALT-2 studies show that tolvaptan does correct hyponatraemia in this patient population when used for a month. If continuous treatment with tolvaptan is required it should be interrupted at intervals in order to reassess the need for continuation. Sub-group analysis has only been reported for patients with SIADH so it is unknown whether tolvaptan is equally as effective in the other subgroups of patients with chronic heart failure and liver cirrhosis. There were many exclusion criteria, which may preclude the use of tolvaptan in patients with these excluded conditions (and which are reflected in the SmPC). The study was carried out without mandated fluid restriction or a change in the patient’s medication, including diuretics, which are more likely to be used in patients with chronic heart failure and cirrhosis. The data from patients receiving diuretics was not analysed separately. Almost a quarter of patients taking tolvaptan withdrew from the study, as did a third on placebo. Apart from the number who withdrew due to adverse events, no comment is made for the others. Whether tolvaptan improves the overall prognosis and what the longer term effects are, are yet to be seen.
### Table 2: Results of SALT 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>SALT 1</th>
<th>SALT 2</th>
<th>P value</th>
<th>SALT 1</th>
<th>SALT 2</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary endpoint: change in mean AUC for serum sodium mmol/L</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All patients – Day 4</td>
<td>3.62±2.28</td>
<td>0.25±2.08</td>
<td>&lt;0.001</td>
<td>4.33±2.87</td>
<td>0.42±2.56</td>
<td>&lt;0.001</td>
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<tr>
<td>All patients - Day 30</td>
<td>6.22±4.10</td>
<td>1.66±3.59</td>
<td>&lt;0.001</td>
<td>6.20±3.92</td>
<td>1.84±3.83</td>
<td>&lt;0.001</td>
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<tr>
<td>Mild hyponatraemia Day 4</td>
<td>2.52±1.95</td>
<td>-0.32±2.27</td>
<td>&lt;0.001</td>
<td>3.59±2.34</td>
<td>0.18±2.01</td>
<td>&lt;0.001</td>
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<tr>
<td>Mild hyponatraemia Day 30</td>
<td>3.87±3.01</td>
<td>0.68±2.78</td>
<td>&lt;0.001</td>
<td>4.68±2.91</td>
<td>0.94±2.89</td>
<td>&lt;0.001</td>
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<td>Marked hyponatraemia day 4</td>
<td>4.56±2.88</td>
<td>0.76±1.77</td>
<td>&lt;0.001</td>
<td>5.06±3.16</td>
<td>0.7±2.99</td>
<td>&lt;0.001</td>
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<td>Marked hyponatraemia day 30</td>
<td>8.24±3.84</td>
<td>2.54±4.01</td>
<td>&lt;0.001</td>
<td>7.60±4.31</td>
<td>2.72±4.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Absolute change in serum sodium – mmol/L</strong></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>128.5±4.5</td>
<td>128.7±4.1</td>
<td>129.0±3.5</td>
<td>128.9±4.5</td>
<td></td>
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<tr>
<td>Day 4 – mean</td>
<td>133.9±4.8</td>
<td>129.7±4.9</td>
<td>&lt;0.001</td>
<td>135.3±3.6</td>
<td>129.6±5.2</td>
<td>&lt;0.001</td>
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<tr>
<td>Day 30 – mean</td>
<td>135.7±5.0</td>
<td>131.0±6.2</td>
<td>&lt;0.001</td>
<td>135.9±5.9</td>
<td>131.5±5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Category of hyponatraemia at days 0, 4 and 30, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline: mild</td>
<td>49/102 (48)</td>
<td>51/103 (50)</td>
<td>64/123 (52)</td>
<td>62/120 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: marked</td>
<td>53/102 (52)</td>
<td>52 /103 (50)</td>
<td>59/123 (48)</td>
<td>58/120 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4: normal</td>
<td>38/95 (40)</td>
<td>12/89 (13)</td>
<td>&lt;0.001</td>
<td>65/118 (55)</td>
<td>12/114 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 4: marked</td>
<td>12/95 (13)</td>
<td>44/89 (49)</td>
<td>&lt;0.001</td>
<td>12/118 (10)</td>
<td>46/116 (40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 30: normal</td>
<td>50/95 (53)</td>
<td>22/89 (25)</td>
<td>&lt;0.001</td>
<td>69/118 (58)</td>
<td>28/114 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 30: marked</td>
<td>7/95 (7)</td>
<td>31/89 (35)</td>
<td>&lt;0.001</td>
<td>18/118 (15)</td>
<td>37/114 (32)</td>
<td>0/002</td>
</tr>
<tr>
<td><strong>Fluid status (mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output day 1</td>
<td>3218±1646</td>
<td>2076±1534</td>
<td>&lt;0.001</td>
<td>3185±2543</td>
<td>1914±1366</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluid intake day 1</td>
<td>1825±1057</td>
<td>1492±945</td>
<td>0.04</td>
<td>2129±2110</td>
<td>1705±1396</td>
<td>0.09</td>
</tr>
<tr>
<td>Difference day 1</td>
<td>-1533±1429</td>
<td>-636±1275</td>
<td>&lt;0.001</td>
<td>-1059±1877</td>
<td>-185±870</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pts requiring fluid restriction %</td>
<td>9.3</td>
<td>17.5</td>
<td>0.08</td>
<td>9.2</td>
<td>16.8</td>
<td>0.08</td>
</tr>
</tbody>
</table>

normal sodium: >135mmol/L  mild hyponatraemia: 130-135 mmol/L  marked hyponatraemia: <130mmol/L
Clinical efficacy: Open label study.

Gheorghiade et al carried out a randomised, active-controlled, open-label, dose-titration trial to assess the effect of tolvaptan vs. fluid restriction on serum sodium concentration. The primary objective was to determine if tolvaptan normalised serum sodium concentration, defined as a level ≥135mmol/L or an increase of ≥10% from baseline to the last inpatient assessment. Secondary objectives were change in serum sodium from baseline to last outpatient visit, urine osmolality, urine volume and sodium concentration, body weight, total fluid intake, free water clearance and thirst score (using a 100 point visual analogue scale, 0=not thirsty, 100=most thirsty).

Adults ≥18 years of age with serum sodium <135mmol/L for at least 2 consecutive days and normovolaemia were enrolled. Those with coronary ischaemic events within the last 60 days, a history of sustained ventricular tachycardia/fibrillation or serum creatinine >2.8mg/dL were excluded. Patients were randomised 2:1 to tolvaptan or fluid restriction plus placebo for the duration of their inpatient stay, or 12 days, whichever occurred first. The tolvaptan dose was started at 10mg/day and increased to 15mg, 30mg, 45mg and 60mg as needed to achieve serum sodium concentrations within normal limits. Patients in the fluid restriction arm were initially allowed 1200mL/24hrs; fluid restriction was individualised to achieve serum sodium concentrations within normal limits. Treatment was continued in the outpatient setting if normalisation had occurred within 14 days, otherwise they could be withdrawn from the study to allow for other treatments to be administered. The last dose was given on day 27, and follow up visits scheduled on days 28, 35 and 65.

The authors planned to enrol 75 patients but had to terminate the study early because of enrolment difficulties. A total of 28 patients were enrolled, which the authors’ state was enough to power the study adequately. Hyponatraemia was associated with heart failure in 14 patients, cirrhosis in 4 patients and SIADH in 10 patients. Five subjects were withdrawn in the 2-day run-in phase before randomisation; three in the fluid-restriction group. Fifteen patients were randomised to tolvaptan and eight to fluid restriction plus placebo. Twelve patients received tolvaptan during the outpatient (maintenance) phase, six of these completed the entire 28 days of treatment. Two completed the inpatient phase in the fluid-restriction group and continued the outpatient phase.

During the titration (in-patient) phase the mean dose of tolvaptan used was 26±15mg/day and the mean duration of treatment was 7±3.6 days. The mean dose of tolvaptan taken during the outpatient phase was 28±18mg/day for 14±8 days. At the last inpatient visit significantly larger increases in serum sodium concentrations were seen in the tolvaptan group (5.7±3.2) compared with in the fluid restriction group (1.0±4.7), p=0.0065. At day 65 the mean change in serum sodium was 4.7±3.1mmol/L (tolvaptan) vs. -0.3±4.0mmol/L (fluid restriction), p=0.039. Eleven patients receiving tolvaptan achieved normalisation of serum sodium by the last in-patient visit, compared with three having fluid restriction (p=0.049). This was achieved more rapidly in the tolvaptan group, occurring in 50% by day 4, compared with day 8 in the fluid restricted group (p<0.03). Fluid intake and urine output were greater in the tolvaptan group (as they were not fluid restricted) and there was a trend towards greater decreases in urine sodium and urine osmolality in this group.

There are many limitations to this study: the small number of patients recruited, the number of patients withdrawn and the short term follow-up. The study design required patients to be willing to return for frequent outpatient visits, which affected compliance with study protocol. The cause of hyponatraemia varied among patients and evaluating the response by cause was not possible because of the small patient numbers. Despite the small number and study limitations, the data does suggest that tolvaptan is effective at normalising serum sodium.
**Estimated cost per 100,000 population\(^{12}\)**

Tolvaptan is supplied as packs of 10 x 15mg or 30mg tablets. Each 15mg or 30mg tablet costs £74.68. Dosing starts at 15mg/day and can be increased to a maximum of 60mg/day to achieve the desired serum sodium level.

The economic model below has been supplied by Otsuka Pharmaceuticals (UK) Ltd, the manufacturers of tolvaptan.\(^{12}\) A number of assumptions have been made:

- Budget calculations for the treatment of hyponatraemia secondary to SIADH may be affected by the case mix/number of affected patients of each NHS trust.
- The estimated number of admissions of patients (aged >14 years) with SIADH-induced hyponatraemia were derived from Hospital Episode Statistics (HES) data.\(^{13}\)

Using the methodology and assumptions described, it is estimated that 4 patients (rounded up from 3.9, see table 3) from a referral population of 100,000 would begin treatment with tolvaptan.

Per in-patient medication costs have been based on assumed:

**Table 3: Estimation of number of patients per 100,000 requiring tolvaptan therapy\(^{12}\)**

<table>
<thead>
<tr>
<th>Population size to be considered</th>
<th>100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of population who will be admitted to hospital</td>
<td>26.37%</td>
</tr>
<tr>
<td>Estimated no. of hospital admissions</td>
<td>26,373</td>
</tr>
<tr>
<td>% of admissions</td>
<td>SIADH</td>
</tr>
<tr>
<td>Inpatients with primary diagnosis, % (n)</td>
<td>0.003% (0.9)</td>
</tr>
<tr>
<td>Inpatients with secondary diagnosis, % (n)</td>
<td>0.020% (5.3)</td>
</tr>
<tr>
<td>Patients with hyponatraemia secondary to SIADH, % (n)</td>
<td>100% of 6.2</td>
</tr>
<tr>
<td>Total number of predicted patients</td>
<td>6.2</td>
</tr>
<tr>
<td>Patients admitted who are severely symptomatic and not considered suitable for treatment with tolvaptan, % (n)</td>
<td>10% (0.6)</td>
</tr>
<tr>
<td>No. of pts suitable for treatment with fluid restriction</td>
<td>6.2-0.6 = 5.6</td>
</tr>
<tr>
<td>Patients successfully treated with fluid restriction / symptoms resolve during the ‘treatment period’, % (n)</td>
<td>85% (4.8)</td>
</tr>
<tr>
<td>Patients not managed with fluid restriction alone, % (n)</td>
<td>15% (0.8)</td>
</tr>
<tr>
<td>No. of patients suitable for tolvaptan</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Assumed that 40% of patients have hypo-osmolality & hyponatraemia secondary to SIADH

- Hospital inpatient stay of 16.6 days, with 3 days of fluid restriction prior to tolvaptan.
- Titration period of 4 days followed by 7.6 days of tolvaptan 30mg/day (based on a mean dose of 26 ±15mg and average length of stay for patient with hyponatraemia/SIADH).
- Reduction in hospital stay of 2 days.

On the basis of these assumptions the total acquisition costs of tolvaptan are (for in-patients):

- For the titration period is £298.72
- For the remaining period as an in-patient is £567.57

The predicted total cost of the use of tolvaptan for an in-patient period of care is £866.29 per patient.
In theory, if hyponatraemia was the sole reason for admission, such a patient could be discharged after the titration period of 4 days once serum sodium has normalised. Therefore the predicted total cost of the use of tolvaptan for a 4-day period of in-patient care is £298.72 per patient.

Cost offsets considered in the economic model:

The use of tolvaptan in patients with hyponatraemia secondary to SIADH is potentially associated with cost offsets associated with:

- A reduced length of stay in hospital: 50% of tolvaptan-treated patients were shown to normalise serum sodium within 4 days, compared to 8 days in fluid restricted patients. The average cost/day of in-patient stay is £299. Therefore, the reduction in in-patient costs per patient, due to reduction in length of inpatient stay associated with tolvaptan treatment, is £1,196 for every 2 patients; equivalent to (£598) per patient.
- The reduced need to use demeclocycline and a corresponding reduction in the length of hospital stay due to shorter titration period of tolvaptan. This is based on the assumption that 50% of patients will be switched from demeclocycline to tolvaptan, that the cost of demeclocycline is £2.94 and that demeclocycline would be given for the same period as tolvaptan (13.6 days, for dose titration). The potential reduction in length of stay would be 13.6 – 4 days (titration period) = 9.6 days. The total cost, per in-patient, avoided as a result of the decision to no longer use demeclocycline is: £39.99 drug cost + £2879.40 reduction in hospital stay = £2910.39 per 2 patients; equivalent to (£1455.20) per patient.

Budget impact per 100,000 patients.

Budget Impact of introducing tolvaptan

Based on all the assumptions stated previously, the estimated budget impact of introducing tolvaptan is based on the following:

- 4 patients undergoing treatment with tolvaptan for their initial period of in-patient care
- For calculation of budget impact, the less conservative cost per patient assumption of £866.29 per patient is used for the calculation below.

An additional £3,465.16 would be spent on the prescription of tolvaptan per 100,000 patients per year. This is associated with a potential cost offset of £4,106.39 in reduction in in-patient costs.

Budget Impact - 5 year forecasts

As tolvaptan is a first in class therapeutic agent, it is assumed that the initial uptake in the first year would be 20%, increasing to 80% in 5 years. Thus, the proportional budget impact forecast per 100,000 patients is:

- Year 1 = 0.8 patient = £693.03 (proportional cost offset £821.28)
- Year 5 = 3.2 patients = £2,772.13 (proportional cost offset £3,285.11)

The economic model does not take into account any necessary continued out-patient treatment.
**Reference List**


(3) Schrier RW, Bansal S. Diagnosis and management of hyponatremia in acute illness. Curr Opin Crit Care 2008; 14:627-634.


**Embase**: TOLVAPTAN/ and *HYPONATREMIA/dt [Drug Therapy] [Limit to: Human and English Language]; TOLVAPATAN/ and HEALTH ECONOMICS

**IDIS**: tolvaptan and hyponatraemia; "TOLVAPTAN 40280035" and Descriptor(s): "ECON DRUG ECONOMICS 129" or "ECON COST BENEFIT 130" or "ECON COST EFFECTIVENESS 131" or "ECON COST MINIMIZATION 132" or "ECON COST OF ILLNESS 133" or "ECON COST UTILITY 134"

**Medline**: tolvaptan.af [Limit to: Humans and English Language] and *HYPONATREMIA/dt [Drug Therapy]; tolvaptan.af and ECONOMICS/PHARMACEUTICAL