The East of England
Priorities Advisory Committee
A function of PrescQIPP

GUIDANCE STATEMENT

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

PAC recommendations

Recommendations for SIADH in patients not requiring chemotherapy:

1. Tolvaptan is recommended as an option for treating hyponatraemia secondary to SIADH for patients who do not require chemotherapy with proven SIADH with serum sodium <125 mmol/litre with symptoms or <120 mmol/litre without symptoms, where fluid restriction and a one week trial of demeclocycline treatment have failed or are contraindicated
2. Course of treatment should not exceed 10 days.
3. Treatment should be initiated in secondary care and monitored by a specialist.
4. Prescribing should remain in secondary care. Prescribing in primary care is not recommended.
5. Trusts must notify CCGs on initiation of treatment and provide clinical and outcome data.
6. The responsibility for commissioning tolvaptan for patients requiring chemotherapy is the responsibility of NHS England (NHSE).

Medicine	Tolvaptan for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Proposed sector of prescribing	Secondary care

Background

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) involves the excessive secretion of antidiuretic hormone (ADH) from the posterior pituitary gland or another source. ADH controls water reabsorption by the kidneys' nephrons, causing the retention of water but not solute. Therefore, ADH causes dilution of the blood which decreases the concentration of solutes such as sodium.

Causes of SIADH include:

- Nervous system disorders, e.g. meningitis/subarachnoid haemorrhage (SAH)
- Malignancy, e.g small-cell lung cancer
- Drugs, e.g. carbamazepine/SSRIs/amitriptyline
- Infections, e.g. atypical pneumonia/lung abscess/cerebral abscess
- Hypothyroidism.

Treatment options include fluid restriction and drug treatment with demeclocycline or vasopressin receptor antagonists, e.g. tolvaptan.

Tolvaptan is excluded from the national tariff.[1] Historically, commissioning of tolvaptan was the responsibility of Primary Care Trusts (PCTs). In the absence of national guidance (e.g. NICE Technology Appraisal Guidance), East of England (EoE) PCTs made local policy for its use. Historically, some EoE PCTs supported the use of tolvaptan for hyponatraemia secondary to SIADH where conservative treatment, fluid restriction and demeclocycline have failed.

However, when NHSE was formed, the commissioning responsibility for tolvaptan for the treatment of hyponatraemia and other endocrine uses passed to NHS England (NHSE). NHSE did not support routine commissioning and all requests for use were processed via the NHSE Individual Funding Request (IFR) route.

In April 2016, the responsibility for commissioning tolvaptan changed once again, with NHSE retaining responsibility for commissioning for hyponatreamia in cancer patients, with responsibility for commissioning for other indications returning to Clinical Commissioning Groups (CCGs).[2]

The indications for NHSE drugs list states that NHSE are responsible for commissioning tolvaptan for "hyponatraemia in cancer".[2]

NHSE Clinical Commissioning Policy 16051/P published in December 2016 states that NHSE will only commission tolvaptan for hyponatraemia in cancer patients who require chemotherapy and who meet the following criteria:[3]

- Who have both mild to moderate hyponatraemia (caused by SIADH) and
- Have been delayed in starting chemotherapy due to their hyponatraemia.

Tolvaptan will be routinely commissioned by NHSE when:

1. The patient has mild or moderate biochemical hyponatraemia (serum sodium 125-135mmol/L); AND
2. The patient fulfils the diagnostic criteria for SIADH (as per definitions); AND
3. The treating oncologist confirms that chemotherapy is being delayed due to hyponatraemia secondary to SIADH; AND
4. The use of tolvaptan has been authorised by the locally designated endocrinologist; AND
5. Used for a limited period (maximum of 10 days).

Tolvaptan will not be routinely commissioned by NHSE for:

1. Patients with hyponatraemia from causes other than SIADH; OR
2. Patients with hyponatraemia secondary to SIADH (as per definitions) with a non-malignant cause; OR
3. Patients where treatment of hyponatraemia is proposed for reasons other than limiting delay to cancer chemotherapy; OR
4. Patients with volume depletion; OR
5. Patients with hyponatraemia associated with significant neurological symptoms (e.g. coma, seizure); OR
6. Patients with profound hyponatraemia (serum sodium <125 mmol/L) which may represent a medical emergency; OR
7. Patients with mild hyponatraemia, without significant symptoms in whom the sole aim of treatment is normalising serum sodium concentration.

Summary of evidence for use

An evidence review on the use of tolvaptan for hyponatraemia secondary to SIADH was undertaken by London and South East Regional Medicines Information on behalf of Bedfordshire and Luton Joint Prescribing Committee, Appendix A.

The evidence presented in the review does not support the use of tolvaptan in SIADH.

A European Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia was published in 2014 and this does not support use of pharmacological intervention (including the use of demeclocycline or tolvaptan) for the management hyponatraemia due to SIADH. The recommendations included in the guideline state:

- Fluid restriction is first-line treatment.
- Increased intake of osmotic solutes (using oral urea) to enhance clearance of water is a second-line treatment.
- For demeclocycline and lithium, there is some evidence of possible harm and their use for management of any degree of chronic hyponatraemia in patients with SIADH is not recommended.
- Although vasopressin receptor antagonists do increase serum sodium, based on current evidence, these drugs cannot be recommended. The risk benefit ratio seems to be negative in that there is no proven outcome benefit aside from increase in serum sodium concentrations and there are increasing concerns about safety. The most prominent safety-related factor is the increased risk for overly rapid correction of hyponatraemia. In addition, the concern around the toxicity profile of these compounds has been increased by reports from the US FDA warning about the risk of hepatotoxicity associated with the use of high tolvaptan doses in autosomal dominant polycystic kidney disease.

However it is acknowledged that the European guidelines do not reflect UK practice as both demeclocycline and tolvaptan are used within the UK for this indication.

Treatment alternatives and place in therapy

Fluid restriction is first-line treatment for the treatment of hyponatraemia secondary to SIADH. In practice fluid restriction may not always resolve hyponatremia in a timely fashion and restricting fluids for an extended period of time may cause significant discomfort for the patient, and may delay discharge.

The European Clinical Practice Guideline on treatment of hyponatraemia recommend increasing intake of osmotic solutes (using oral urea) to enhance clearance of water as a second-line treatment, however this is not an option in the UK as these products are not commercially available.

The use of demeclocycline is not supported by the guidelines but it is used in clinical practice in the UK. It is associated with GI disturbance, renal toxicity and gives an unpredictable response with a slow onset of action. There have been supply problems with demeclocycline over the past few years and although licensed demeclocyline is currently available again, the cost has risen significantly. Feedback from EoE clinicians was in favour of a one week trial of demeclocycine if fluid restriction has failed.

Feedback from EoE clinicians indicates that, despite the lack of evidence to support use, there was a place for using tolvaptan in the following patient groups:

- Patients with proven SIADH who do not require chemotherapy with serum sodium <125 mmol/litre with symptoms or <120 mmol/litre without symptoms, where fluid restriction and demeclocycline treatment have failed or are contraindicated.[4]

Clinicians have indicated that, in practice, a short course of a few days (up to a maximum of 10 days) is required to normalise sodium levels which can then be more readily managed by fluid restriction.

Intractable hyponatraemia may prevent discharge in patients who are otherwise suitable for discharge. Whilst tolvaptan is a high cost treatment (£74.68 to £149.36 per day), this would be offset by any reduction in a patient's length of stay. More timely discharge is of particular value for end of life patients where hyponatraemia is delaying their discharge from hospital to home, or to their chosen place of care.

It is acknowledged that there are safety concerns over the use of tolvaptan, but these can be minimized by the use of short courses. It is also noted that the risk/benefit axis shifts in favour of benefit when considering use of tolvaptan in end of life patients, as improvement in symptom control may outweigh any concerns about toxicity.

Due to the risk of over rapid correction of serum sodium levels, treatment should be initiated by a specialist and take place in hospital or in a setting where the patient can be closely monitored for over rapid correction of hyponatraemia (e.g. hospice).

Because of the need for timely treatment of hyponatraemia, it is acknowledged that the IFR route would not be a suitable route for obtaining approval to treat patients with acute hyponatremia due to SIADH.

On initiating treatment with tolvaptan acute trusts should notify CCGs and provide clinical details and outcome data via an agreed proforma.

Formulation/available products/licensed indication/usual dosage

SPC Samsc[5]

Formulations:

Samsca 15mg tablets: Each tablet contains 15mg tolvaptan.

Samsca 30mg tablets: Each tablet contains 30mg tolvaptan.

Therapeutic indications

Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Posology and method of administration

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status (see section 4.4 of the SPC), treatment with Samsca should be initiated in hospital.

Posology

Treatment with tolvaptan should be initiated at a dose of 15mg once daily. The dose may be increased to a maximum of 60mg once daily as tolerated to achieve the desired level of serum sodium. During titration, patients should be monitored for serum sodium and volume status (see section 4.4). In case of inadequate improvement in serum sodium levels, other treatment options should 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 (see sections 4.4 and 4.5). For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels should be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatraemia, 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 hyponatraemia is no longer a clinical issue.

Costs and tariff status

Tariff status: Tolvaptan is included on the National Tariff list of excluded high cost drugs and is therefore excluded from tariff.[1]

Cost: Tolvaptan 15mg or 30mg tablet: £74.68 per tablet (Appendix A)

Tolvaptan dose	7 days treatment	10 days treatment
15mg od	£522.76	£746.80
30mg od	£522.76	£746.80
60mg od	£1,045.52	£1,493.60

National guidance

None

Decisions from other bodies

None from NICE, SMC, AWMG.

NHSE Clinical Commissioning Policy: Tolvaptan for hyponatraemia secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in patients requiring cancer chemotherapy.[3]

Comments sought from

East of England clinicians via PAC members.

Author: Joanne Lowe on behalf of PAC

Document history

PAC approval date	10 July 2017
Version	v1
Consultation process	East of England clinicians PAC members
QA process	Sue Smith. Senior Clinical Pharmacist, PrescQIPP, 17 August 2017

References

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2. Indications for NHSE drugs list version 12 published April 17 https://www.england.nhs.uk/commissioning/spec-services/key-docs/
3. NHSE Clinical Commissioning Policy: Tolvaptan for hyponatraemia secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in patients requiring cancer chemotherapy. Reference: NHSE: 16051/P Published December 2016 https://www.england.nhs.uk/commissioning?s=tolvaptan
4. Colchester University hospital guidelines for the use of Tolvaptan (Samsca®) available on request
5. Summary of Product Characteristics. Samsca 15mg and 30mg tablets, Otsuka Pharmaceuticals (UK) Last Updated 05-Aug-2014. Accessed 25/10/16 via https://www.medicines.org.uk/emc/medicine/22210

Assessment against ethical and commissioning principles

Treatment assessed	Tolvaptan (Samsca®) for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
East of England Priorities Advisory Committee recommendation	1. Tolvaptan is recommended as an option for treating hyponatraemia secondary to SIADH for patients who do not require chemotherapy with proven SIADH with serum sodium <125 mmol/litre with symptoms or <120 mmol/litre without symptoms, where fluid restriction and a one week trial of demeclocycline treatment have failed or are contraindicated. 2. Course of treatment should not exceed 10 days 3. Treatment should be initiated in secondary care and monitored by a specialist. 4. Prescribing should remain in secondary care. Prescribing in primary care is not recommended. 5. Trusts must notify CCGs on initiation of treatment and provide clinical and outcome data. 6. The responsibility for commissioning tolvaptan for patients requiring chemotherapy is the responsibility of NHSE.
Clinical effectiveness	The evidence for efficacy and safety is not in favour of routine use. However, there is a group of patients who do not respond to first and second line treatment for whom use would be appropriate to relieve symptoms and reduce length of stay as an inpatient.
Cost effectiveness	Unknown.
Equity	No issues identified
Needs of the community	There is a lack of data on cost-effectiveness, however the cost of the treatment is likely to be offset by a reduction in the patient's length of stay, and therefore should not result in the need for disinvestment in other areas.
Need for healthcare (incorporates patient choice and exceptional need)	A small group of patients who do not respond to first and second line therapies would benefit from this treatment.
Policy drivers	None identified
Disinvestment	None identified

Appendix A: Update to 2009 review on tolvaptan (Samsca) for hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH)

Review conducted for Bedfordshire and Luton Joint Prescribing Committee by London and South East Regional Medicines Information (Aug 2016)

Summary

Since the 2009 review, there have been new data from a subgroup analysis of the SIADH population in the SALT trials; as well as from four year open-label extension of these trials (SALTWATER). Lower level data from observational studies and case reports/series are not discussed. No RCTs of tolvaptan vs. other active treatments were identified.

The results of a subgroup analysis confirm that the efficacy and safety results reported previously for the mixed hyponatraemia population in SALT-1 and SALT-2 were applicable to patients with a diagnosis of SIADH as well. Data from SALTWATER long term follow-up indicate that mean serum sodium levels remained within the normal range throughout the subsequent four year treatment period after the initial titration period, with ~50% of patients in mild and marked hyponatremia groups exhibiting normal serum sodium levels by week four. Mean dose of tolvaptan increased to ~30mg/d during the first 16 to 20 weeks and remained at that level throughout the remainder of the study. In all patient subgroups, serum sodium levels declined after seven days of withholding tolvaptan. Most patients (95%) experienced an adverse event (AE) and six patients discontinued treatment due to an AE. Eighteen patients had serum sodium levels >145 mmol/L at individual time points, of which one was withdrawn from the trial; hypernatraemia resolved in the other 17 patients.

European guidelines on hyponatraemia published in 2014 do not recommend the use of vasopressin receptor antagonists for SIADH because of the risk/benefit ratio, in that there is no proven outcome benefit aside from increase in serum sodium concentrations with use of these agents and there are increasing concerns about safety. The most prominent safety-related factor was the increased risk for overly rapid correction of hyponatraemia. Furthermore, the concern around the toxicity profile of these compounds has been increased by warnings from the US FDA about the risk of hepatotoxicity associated with the use of high tolvaptan doses in another condition; autosomal dominant polycystic kidney disease. Interestingly this guideline does not support use of any pharmacological treatment in SIADH.

Licensed demeclocycline capsules are back in stock. It should be noted that its cost has significantly increased since the last review was done (28 x 150mg capsules now costs ~£161) and may now be more expensive than the unlicensed product. However, it is less costly than tolvaptan (28 days tolvaptan 30mg/day ~£2100 vs. £966-£1288 for 900-1200mg/day demeclocycline).

SALT 1 and SALT 2 studies

The pivotal SALT studies recruited 424 patients with euvolaemic or hypervolaemic hyponatraemia (serum sodium <135 mmol/L) due to a variety of underlying causes (heart failure, liver cirrhosis, SIADH and others). They were treated for 30 days with tolvaptan (n=216) or placebo (n=208) at an initial dose of 15mg/day. The primary endpoint for these trials was the average daily AUC for change in serum sodium from baseline to day 4 and baseline to day 30. Tolvaptan was superior to placebo ($p<0.0001$) for both periods in both studies. At seven days after discontinuing treatment, sodium values decreased to levels of placebo treated patients. Following three days of treatment, the pooled analysis of the two trials revealed five-fold more tolvaptan than placebo patients achieved normalisation of serum sodium concentrations (49% vs. 11%). This effect continued as on day 30, when more tolvaptan than placebo patients still had normal concentrations (60% vs. 27%). These responses were seen in patients independent of the underlying disease.[1]

New evidence

Since the last review (2009), no RCTs comparing tolvaptan with other active treatments were identified. The only new data consisted of further analyses of participants of the SALT studies. Lower level evidence from observational studies were not addressed due to availability of RCT data from the SALT studies.

Subgroup analysis of SIADH population in SALT 1 and SALT 2 studies2

This analysis of 110 (n=52 tolvaptan, 58 placebo) patients, half of whom had marked hyponatremia (<130 mmol/l) reported that improvement in serum sodium was significantly greater (p<0.0001) with tolvaptan than placebo over the first 4 days of therapy (5.28 vs. 0.47 mmol/l, respectively) as well as over the entire 30-day study (4.55 vs. 1.89 mmol/l). In the tolvaptan group, mean serum sodium rose to >135 mmol/l in ~3–4 days and remained there throughout the treatment phase. In the placebo group, serum sodium remained <135 mmol/l throughout the study period. Withdrawal of tolvaptan resulted in the reestablishment of baseline hyponatremic serum sodium within seven days, consistent with the results of the earlier SALT studies. Overall, 5.9% of tolvaptan-treated patients had overly rapid correction of hyponatremia. Increased thirst, dry mouth, and urination were reported as side effects. Patient's self-assessed health status was determined at baseline and day 30 using the SF-12 General Health Survey. Over the 30-day study period, the tolvaptan group showed a statistically significantly greater improvement on the physical component than the placebo group, but there was no significant difference on the mental component of the survey.

In the tolvaptan and placebo groups, 10 (19%) and 16 (28%) patients respectively discontinued from the trial before completing the 30-day treatment period. Of these, 5 (10%) on tolvaptan and 7 (12%) on placebo withdrew specifically for adverse experiences. No patient in the tolvaptan group experienced a serious adverse event considered by the investigator to be related to study medication Of the 51 patients treated with tolvaptan, 3 (5.9%) exceeded protocol recommended correction limits of an increase in serum sodium >12 mmol/l over the first 24 hours of correction and >18 mmol/l over the first 48 h of correction. All three patients with overly rapid correction had marked hyponatremia (baseline serum (<130 mmol/l) and none of them were reported to exhibit any neurological symptoms suggestive of osmotic demyelination.

Overall, these data were considered to confirm that the efficacy and safety results reported previously for the mixed hyponatremia population in SALT-1 and SALT-2 were applicable to patients with a diagnosis of SIADH as well.

The Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER)[3]

This was a four year sequential, open-label extension of the SALT-1 and SALT-2 studies assessing whether tolvaptan maintained its safety (primary objective) and efficacy over a prolonged period in patients who had hyponatremia and were treated with a flexible-dosage regimen. Preliminary results of SALTWATER were provided to US and European regulatory authorities in their consideration of the eventual approval of tolvaptan.

Study population

A total of 154 of 325 patients who had hyponatremia and completed the 30 day treatment phase and 7 day follow-up period in SALT-1 and SALT-2 were at sites participating in SALTWATER. Of these, 111 (38 patients from SALT-1 and 73 fromSALT-2) enrolled in the open-label SALTWATER extension and received treatment. Sixty-four of enrolled patients discontinued during the follow-up period, and of these, 2 were lost to follow-up, 3 were withdrawn at sites closed by the sponsor, 7 met withdrawal criteria, 9 did not re-enroll after either the first- or the second-year extension, 13 withdrew consent, and 30 discontinued because of an AE or death. All 111 patients were analysed for safety, and 110 patients were analysed for efficacy. Because patients who had been on active drug and placebo during the SALT-1 and SALT-2s did not differ significantly from one another, they were analysed together in

the open-label trial. Fifty-two (46.8%) patients had had mild hyponatremia (serum sodium ≥130 and <135 mmol/L), and 59 (53.2%) had had marked hyponatremia (<130 mmol/L) in SALT-1 and SALT-2 at baseline. 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. Mean dosage of tolvaptan increased to approximately 30mg/d during the first 16 to 20 weeks and remained at that level throughout the remainder of the study

Efficacy

The mean serum sodium concentration in all 111 patients at baseline in SALTWATER was 130.8mmol/L (range 114 to 141 mmol/L). Correction of serum sodium levels during the first 8 hours of therapy occurred at similar rates in SALTWATER and SALT-1 and SALT-2. After the initial titration period, mean serum sodium levels remained within the normal range throughout the subsequent four year treatment period.

The following findings were noted:

- More than 60% and 45% of patients in the mild and marked hyponatremia groups, respectively, exhibited normal serum sodium levels by week 4. Correction rates seemed to be generally similar among patients with CHF and SIADH/other but may have been somewhat lower among patients with cirrhosis.
- In all patient subgroups, serum sodium levels declined by 7 days of withholding tolvaptan, suggesting that continued tolvaptan may be needed to maintain serum sodium normalisation in many patients. On drug discontinuation, the proportion of patients who declined by at least 3mmol/L was 68%, and an equal proportion fell from 135mmol/L to below this threshold of normal.
- Mean time to first fluid restriction was 122.3 and 162.5 days in the mild and marked hyponatremia subgroups, respectively; 13.2% of patients in the mild hyponatremia group and 5.4% in the marked hyponatremia group required fluid restriction.
- One (0.9%) patient received urea, and no patients received demeclocycline.

Safety

Mean follow-up time on tolvaptan therapy during SALTWATER was 701 days per patient. During this time, 105 of 111 (~95%) patients experienced an AE. The most common AEs assessed by the investigator as being potentially related to tolvaptan use were pollakiuria (frequent daytime urination, n=11); thirst (n=10); fatigue (n=6); and dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral oedema, and acute renal failure (4 patients each). Six AEs leading to drug discontinuation were assessed by the investigator as possibly or probably related to tolvaptan 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). No consistent and clinically meaningful changes were observed in vital signs, ECG, serum chemistries (other than serum sodium and chloride), or haematology during the follow-up period. Serum sodium correction exceeded the desirable rate of 1 mmol/L per h at the 8-hour time point in 5 patients. Eighteen patients had serum sodium levels >145 mmol/L at individual time points. One of the latter patients was withdrawn from the trial for mild serum sodium increase; the hypernatremia resolved in the other 17 patients.

It was concluded from these findings that prolonged administration of tolvaptan (4-years) maintains an increased serum sodium with an 'acceptable' margin of safety.

Guidelines

There are no guidelines from NICE/SMC/AWMSG on tolvaptan for hyponatraemia secondary to SIADH.

A European Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia

was published in 2014. Interestingly, this does not support use of pharmacological intervention for management hyponatraemia due to SIADH. It makes the following recommendations:[4]

- Fluid restriction is first-line treatment.
- Increased intake of osmotic solutes (using oral urea) to enhance clearance of water is a second-line treatment.
- For demeclocycline and lithium, there is some evidence of possible harm and their use for management of any degree of chronic hyponatraemia in patients with SIADH is not recommended.
- Although vasopressin receptor antagonists do increase serum sodium, based on current evidence, these drugs cannot be recommended. The risk/benefit ratio appears negative in that there is no proven outcome benefit aside from increase in serum sodium concentrations and there are increasing concerns about safety. The most prominent safety-related factor is the increased risk for overly rapid correction of hyponatraemia. In addition, the concern around the toxicity profile of these compounds has been increased by reports from the US FDA warning about the risk of hepatotoxicity associated with the use of high tolvaptan doses in autosomal dominant polycystic kidney disease.

Drug costs[5]

The cost of tolvaptan remains the same as in 2009. However, the cost of licensed demeclocycline capsules (last documented in the 2009 review as £2.94 per day for 900mg dose) has increased. Unlicensed 150mg demeclocycline tablets are also available from importers, however licensed demeclocycline may now be more expensive than the unlicensed product since the price increase.

Drug	Unit cost	28 days
Tolvaptan 15 or 30mg	£74.68 per tablet	£2,100
Demeclocycline 150mg	£5.75 per capsule	£966 (900mg daily dose) £1,288 (1200mg daily dose)

No British cost-effectiveness data were identified.

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