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NHS England

Clinical Commissioning Policy Proposition:

Tolvaptan for hyponatraemia secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in patients requiring cancer chemotherapy

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Tolvaptan for hyponatraemia secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in patients requiring cancer chemotherapy

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Prepared by NHS England Specialised Services Clinical Reference Group for **Specialised Endocrinology**

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Plain Language Summary

Hyponatraemia is the medical term for low sodium levels in the blood. This condition is very common, affecting approximately 30% of hospitalised patients. Mild hyponatraemia may give no symptoms and resolve spontaneously. Severe hyponatraemia is known to be associated with increased death rates and prolonged hospitalisation.

Early symptoms of hyponatraemia include headache, nausea, vomiting, and general malaise. More advanced signs include confusion, agitation and drowsiness. In extreme cases there may be seizures, respiratory depression, coma and death. Hyponatraemia must therefore be taken seriously and managed well.

An important cause of hyponatraemia is the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) which can affect approximately 35% of hyponatraemic patients. There are various causes of SIADH, which leads to over-dilution of the blood and resulting low sodium levels. In most cases, hyponatraemia can be treated sufficiently with fluid restriction however this is normally a slow response and compliance varies. Tolvaptan is an oral medication which blocks the action of a hormone and reduces the amount of water reabsorbed by the kidneys, which improves sodium levels. Tolvaptan is only licenced for use in patients with mild or moderate hyponatraemia.

Chemotherapy for cancer requires patients to be well hydrated which in itself can cause hyponatraemia. These dangerously low sodium levels can go on to cause seizures. In these patients, hyponatraemia may be delaying the start of chemotherapy putting the patient at further harm and it is in this situation where tolvaptan has a role.

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of tolvaptan for patients with mild to moderate hyponatraemia secondary to SIADH, in whom initiation of chemotherapy is delayed as a result of the hyponatraemia.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission tolvaptan for hyponatraemia secondary to SIADH.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether tolvaptan will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Hyponatraemia (serum sodium <135 mmol/L) is common, affecting up to 30% of hospitalised patients. In 35% of these patients, hyponatraemia is attributed to the Syndrome of Inappropriate Antidiuresis (SIADH). SIADH is characterised by the continued production of the hormone vasopressin (AVP) at plasma osmolalities below the normal osmotic threshold for AVP release, leading to increased renal water resorption through activation of AVP-dependent water channels in the distal nephron. Profound biochemical hyponatraemia resulting in significant symptoms and signs is a medical emergency, treated with hypertonic fluid under close supervision. However, the majority of clinical situations involve less profound hyponatraemia, together with symptoms and signs that are less marked. Treatment of the precipitating cause of SIADH, together with fluid restriction, is the common first-line approach in this situation. Demeclocycline has been used in patients with refractory SIADH. However, its utility is limited by adverse effects (gastrointestinal upset, photosensitivity and renal toxicity), unpredictable response, delayed onset of action and limited availability.

Hyponatraemia is common in cancer patients, especially those with lung cancers, some of which secrete AVP leading to worsening hyponatraemia. Small cell lung cancer is notorious for causing SIADH although other cancers also lead to this syndrome. This policy concerns patients with mild to moderate hyponatraemia secondary to SIADH, where the hyponatraemia is preventing chemotherapy from proceeding. Chemotherapy requires adequate pre-hydration which often causes a dilutional hyponatraemia. This hyponatraemia can lead to seizures and so a normal serum sodium level is required prior to commencing chemotherapy. It is in these patients that fluid restriction would be ineffective and contraindicated. It is also in this subgroup of patients that randomised controlled trials would, for ethical reasons, not be possible and thus the ability to gather sufficient evidence is limited and clinical consensus must be used to give context to the evidence demonstrated. Whilst the evidence outlined in this policy demonstrates the efficacy of tolvaptan in increasing sodium concentration, the evidence does not however provide a framework to highlight the clinical significance of this rise in sodium concentration. Tolvaptan is proposed in patients with malignant disease, where chemotherapy is being delayed due to hyponatraemia.

Tolvaptan (Samsca) is an orally acting, selective vasopressin V2 receptor antagonist that blocks the binding of vasopressin to V2 receptors in the collecting duct of the kidney, reducing water reabsorption. The resulting aquareis addresses the dilutional hyponatraemia that is the central feature of SIADH. The maximum rate of change of sodium concentration occurs in the first 24 hours of treatment. The usual treatment regime with tolvaptan would last a maximum of four to ten days and it is not anticipated to be used for medium or long-term treatment of hyponatraemia. This policy concerns the use of tolvaptan for mild or moderate hyponatraemia, not severe or profound hyponatraemia, in alignment with the licence.

3. Definitions

Hyponatraemia:
Serum sodium that is below the laboratory reference range, commonly less than 135 mmol/L. The degree of biochemical hyponatraemia can be further classified as mild (130-135 mmol/L), moderate (125-129 mmol/L), or profound / severe (less than 125 mmol/L). The degree of biochemical hyponatraemia may not parallel overall clinical status as some patients with profound biochemical hyponatraemia may be relatively symptom-free, while some with moderate biochemistry may have significant neurological symptoms and signs.

Syndrome of Inappropriate Antidiuretic Hormone (SIADH):
A condition characterised by dilutional hyponatraemia due to the inappropriate production and action of vasopressin. The key diagnostic features of SIADH are:
• patient clinically euvolaemic
• plasma sodium concentration <135 mmol/l
• plasma osmolality <280 mOsmol/kg
• urine osmolality > 100 mOsmol/kg
• urinary sodium concentration >30mmol/L
• absence of clinical or biochemical features of adrenal and thyroid dysfunction.
• no diuretic use (recent or past)

Tolvaptan:
An orally acting selective V2 receptor antagonist that blocks the binding of vasopressin to V2 receptors in the collecting duct of the kidney. Licenced for use in mild or moderate hyponatraemia only.

4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on tolvaptan as part of the treatment pathway for adult patients with hyponatraemia secondary to SIADH.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with hyponatraemia secondary to SIADH.

5. Epidemiology and needs assessment

Hyponatraemia is common, affecting up to 15-30% of hospitalised patients and is more common in the elderly population (Upadhyay et al, 2006). SIADH is the most common cause of hyponatraemia representing 35% of all hyponatraemic patients (Hoorn et al, 2006). There is increased mortality, length of hospital stay and readmission rates in patients with hyponatraemia associated with a wide range of co-morbid conditions.

Mild biochemical hyponatraemia due to SIADH often resolves with fluid restriction or treatment of the underlying condition. Moderate biochemical hyponatraemia due to SIADH may be refractory to fluid restriction, or respond slowly. Patients in this group, that have not responded to fluid restriction, may benefit from treatment with tolvaptan if there is a pressing need to normalise sodium for commencement of chemotherapy.

Whilst it is difficult to quantify how many patients will have chemotherapy delayed due to hyponatraemia, one centre estimates that there are 500 new cases of lung cancer diagnosed each year, of which 10-15% (50 - 75) are small cell lung cancer. Of these patients, an estimated 5% (3 - 4) patients each year will have SIADH preventing chemotherapy from commencing thus requiring tolvaptan (Leicester University Hospital NHS Trust).

6. Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of tolvaptan for hyponatraemia secondary to SIADH in patients with malignancy where chemotherapy is being delayed. The evidence does show tolvaptan to be efficacious at increasing serum sodium concentration in patients with mild to moderate hyponatraemia secondary to SIADH. There is also evidence relating to severe hyponatraemia however this was outside the scope of the evidence review as tolvaptan is licenced only for mild to moderable hyponatraemia.

Summary

The evidence of effectiveness of tolvaptan (for short-term treatment of mild to moderate hyponatraemia) is mainly based on two well-designed prospective studies and a small number of case series from the UK. The first is an extension study of patients from the original Study of Ascending Levels of Tolvaptan in Hyponatraemia (SALT1 and SALT2) studies. Verbalis et al (2011) (Level 1++ evidence), report on a sub-group analysis of patients from the original SALT1 and SALT2 trial with 'Syndrome of Inappropriate ADH secretion' (SIADH), which can arise from various causes including malignancy, central nervous system pathology, certain medications and other factors. The other is a double blind randomised controlled trial (RCT) conducted in 37 Chinese patients with hyponatraemia secondary to SIADH (placebo=18, tolvaptan=19) by Chen et al 2014 (Level 1+ evidence). In addition, a US cost-effectiveness study by Dasta et al (2012) (Level 1 evidence) sought to evaluate the potential hospital cost savings associated with tolvaptan usage among patients with the SIADH based on the SALT1 and SALT2 trials by constructing a cost-offset model to evaluate the impact of tolvaptan on hospital resource usage, mainly the length of stay (LOS). Although LOS was lower for patients treated with tolvaptan compared to placebo, this was not statistically significant (see part 3 below for details).

Both prospective studies indicated that tolvaptan has a prompt biochemical effect improving serum sodium concentration (so addressing hyponatraemia), and that this reduces the need for fluid restriction, allowing patients to have a more normal fluid intake. Whilst this would theoretically reduce the need for hospital admission or prolongation of an existing stay, Dasta et al (2012) did not confirm this at a level of statistical significance.

Detailed Evidence

Part 1: Clinical Effectiveness

Verbalis et al (2011) analysed of a subgroup of 110 patients with a primary diagnosis of SIADH from the original SALT studies, assigned to either tolvaptan 15-30mg daily (52) or oral placebo (58). In each treatment group, 42 patients completed the full 30-day treatment period. Another smaller subgroup of SIADH patients (based on urine sodium concentration) was also identified and reviewed (24 patients in the tolvaptan group and 25 patients in the placebo group).

The primary outcomes were the change in the average daily area under curve (AUC) for the serum sodium concentration from baseline to both day four and to day 30. In the SIADH subgroup, patients on tolvaptan had highly significant ($P<0.0001$) improvements in serum sodium concentrations relative to the placebo group at day 4 (5.28±3.35mmol/L vs 0.47±2.81mmol/L respectively) and day 30 (8.07±4.55mmol/L vs 1.89±4.13 mmol/L). The smaller subgroup of SIADH patients showed similar results at day four (4.61±1.97mmol/L vs 0.96±2.78mmol/L; $P<0.0001$) and day 30 (6.28 ±3.17mmol/L vs 2.03±4.37mmol/L; $P<0.0001$). Withdrawal of tolvaptan therapy resulted in the re-establishment of baseline hyponatremia (serum sodium concentration) within seven days.

This study also reported that patients treated with tolvaptan were managed in an outpatient setting without fluid restriction, avoiding the need for hospital admission to fluid restrict patients and monitor urine output. Relative to the placebo group, the tolvaptan group had both larger mean fluid intake (2016±1234ml vs 1563±966 ml; $P=0.049$) and larger mean urine output (3057±1701ml vs 1758±928 ml; $P<0.001$).

The study by Chen et al (2014) is a double-blind RCT with good study methodology including randomisation, patient selection criteria, and statistical analysis. The results show the tolvaptan group (15-60mg daily) had better outcomes for the primary end point. Average daily changes in serum sodium levels from baseline to day four were 1.9±2.9mmol/L (1.9±2.9mEq/L) in the placebo group and 8.1±3.6mmol/L (8.1±3.6mEq/L) in the tolvaptan group, and to day seven were 2.5±3.9mmol/L (2.5±3.9mEq/L) for the placebo group and 8.6±3.9mmol/L (8.6±3.9mEq/L) for the tolvaptan group. The differences between the two groups were significant (ANCOVA, $P<0.0001$) both at days four and seven. Outcomes for secondary endpoints were also positive.

In the context of the research question, the biggest limitation is that neither of the studies analysed outcome results by level of severity of hyponatraemia (e.g. mild, moderate) and the studies excluded patients who were treated with demeclocycline. Therefore generalisation of results to the specific cohort described in the research questions is limited.

Evidence from case series comes from both UK and international studies. A UK study by Tzoulis et al (2015) (Level 3 evidence), is based on real-life experience from patients admitted to a general hospital in the UK. Veghasiya et al (2012) is a European case series comparing the effect of tolvaptan in small number of patients with SIADH and heart failure (both Level 3 evidence).

The study by Tzoulis et al (2015) is a retrospective case study of outcomes for 64 patients with hyponatraemia due to SIADH who were treated with tolvaptan 15-30 mg, either as first line therapy or following other treatments including fluid restriction and/or demeclocycline. The mean serum sodium increase 24 hours after tolvaptan initiation was 9.0±3.9mmol/L. At the end of tolvaptan therapy, serum sodium increase was 13.0±5.9mmol/L with 96.7% of patients having serum sodium increases ≥5mmol/L in 48 hours.

A study by Vaghasiya et al (2012) studied the effect of a single 15mg dose of Tolvaptan in 13 patients with hyponatraemia, of whom 8 patients had SIADH. The mean serum sodium rise was 6.4mmol/L in 24 hours. Three patients, all with SIADH, showed an 8mmol/L rise in serum sodium within 12 hours.

Part 2: Clinical effectiveness versus fluid restriction and/or demeclocycline

There are no head-to-head comparisons of tolvaptan against fluid restriction or demeclocycline in the management of hyponatraemia secondary to SIADH. There is some evidence (Level 3) that tolvaptan is effective in improving serum sodium levels in patients with persistent hyponatraemia following treatment with fluid restriction. Due to small numbers of patients in relevant case series, it is not possible to conclude on the evidence in circumstances where demeclocycline was used.

Tzoulis et al (2015) included patients who had persistent hyponatraemia or failed to correct after initial treatment with fluid restriction (majority) and demeclocycline in small number. In this study, 86% of the patients (52/61) were treated with fluid restriction and/or demeclocycline as a first or second line treatment. Tolvaptan was used as first-line agent in 9/61 cases after failure of other therapeutic modalities including fluid restriction or demeclocycline. This study showed nearly 96.7% of patients having serum sodium increase ≥5mmol/L in 48 hours.

Another limitation in evidence generation for the research question is the lack of standardised protocol for identifying SIADH and treatment of SIADH across hospitals in the UK and other places in the world. This was evident from a study of the hyponatraemia registry by Greenberg et al (2015), which showed that only 47% of the 1,597 patients with SIADH as identified by treating physicians had all three cardinal diagnostic tests performed, and 11% underwent none. The full diagnostic criteria include normal thyroid and adrenal function, but only 21% of identified SIADH patients underwent cortisol and thyroid hormone determinations, along with the required electrolyte and osmolality measurements.

Part 3: Cost effectiveness

There are no studies evaluating the cost effectiveness of tolvaptan in the subset of patients as defined in the research question. However, evidence for cost effectiveness for use of tolvaptan in patients with hyponatraemia due to SIADH comes from a study by Dasta et al (2012). The primary objective of this study was to evaluate the potential hospital cost savings associated with tolvaptan usage among patients with SIADH (based on the SALT1 and SALT2 trials) by constructing a cost-offset model to evaluate the impact of tolvaptan on hospital resource usage, mainly the length of stay (LOS) among patients with the SIADH.

The analysis was conducted from the perspective of hospitals in the United States and the total number of patients admitted with SIADH was obtained from Nationwide Inpatient Sample (NIS). The hospital costs and LOS associated with SIADH was collected from The Healthcare Cost and Utilization Project (HCUP) database for adult (age >18 years) patients with a primary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for the SIADH of 253.6.

The estimates for effectiveness were based on SALT1 and SALT2 results in which the SIADH subpopulation had a significant estimated improvement in serum sodium concentration of 5.28 ± 3.35mEq/L by the fourth day such that 60% of patients with the SIADH receiving tolvaptan had normalised serum sodium levels, in comparison with 11.5% of patients receiving placebo. However, the mean hospital LOS in tolvaptan was lower by 1.21 days (not statistically significant). LOS in tolvaptan (n = 52) was 4.98 ± 6.61 days compared to 6.19 ± 7.89 days in patients who received a placebo (n = 58). The relative difference in LOS due to tolvaptan usage in the SALT1 and SALT2 trials was 19.5%.

The main limitations of the study from the perspective of the research questions were that the cost analysis is based on hospitals in the USA (limiting the ability to draw direct comparison with other health care systems), and that whilst the research question focuses mainly on mild and moderate SIADH, nearly 50% of SIADH patients in the two studies which are used in economic modelling had moderate to severe hyponatraemia defined as Na <130mmol/L. Therefore generalising these results to the population stated in the research questions is limited.

Part 4: Safety

There are no studies evaluating the safety of tolvaptan specifically in the cohort of patients defined in the research question. However, evidence of safety using tolvaptan in hyponatraemia in patients with SIADH is available mainly from the study by Verbalis et al (2011), and very limited data in the case series by Tzoulis et al (2011).

Exceeding protocol-recommended correction limits for serum sodium concentration following tolvaptan treatment is a known complication. In Verbalis et al (2011), of the 51 patients treated with tolvaptan, three (5.9%) exceeded protocol recommended correction limits of an increase in serum sodium >12mmol/L in the first 24 hours of correction and >18mmol/L in the first 48 hours of correction: one with a correction of 13mmol/L and two with a correction of 14mmol/L over the first 24 hours of therapy. All three of the patients with overly rapid correction had marked hyponatraemia (baseline serum [Na+] <130mmol/L).

Slightly higher rates were seen in study by Tzoulis et al (2015) where 18% (10/61) had more than recommended correction at 24 hours and 21% at 48 hours.

Thirst and dry mouth were the most common tolvaptan-related adverse events in the SALT trials. In the study by Verbalis et al (2011), these adverse events were relatively similar between the two treatment groups and occurred in 9 (18%) and 8 (16%) patients respectively on tolvaptan and 5 (9%) and 6 (10%) patients respectively on placebo in this SIADH subgroup analysis. However the potentially drug-related adverse events of dizziness, vomiting, hypotension, and nasopharyngitis occurred at slightly higher rates in the placebo group.

In the study by Verbalis et al (2011), 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, five patients (10%) on tolvaptan and seven patients (12%) on placebo withdrew specifically for adverse experiences.

Verbalis et al (2011) reported four deaths (one in the tolvaptan group and three in the placebo group). None of the deaths were considered to be treatment related. Tzoulis et al (2015) reported five deaths but it is not clear how many of them were linked to Tolvaptan.

In the main, short-term treatment with tolvaptan is usually well-tolerated.

7. Proposed criteria for commissioning

Tolvaptan will be routinely commissioned by NHS England when:

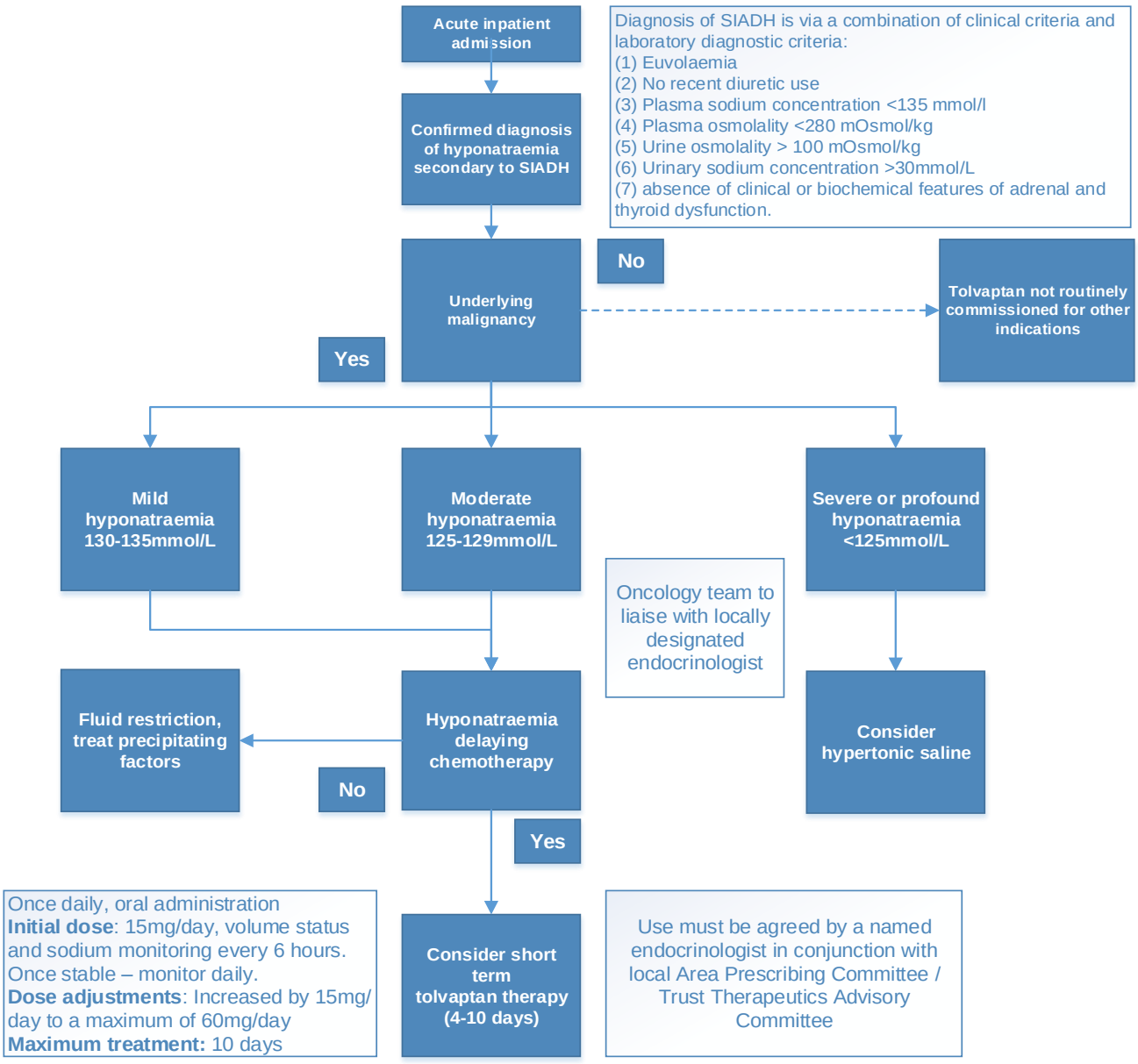
(1) The patient has mild or moderate biochemical hyponatraemia (serum sodium 125-135mmol/L)
(2) The patient fulfils the diagnostic criteria for SIADH (as per definitions)
(3) The patient has an underlying diagnosis of malignancy where the treating oncologist confirms that chemotherapy is being delayed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

Tolvaptan will not be routinely commissioned by NHS England for:

(1) Patients with hyponatraemia from causes other than SIADH.
(2) Patients with hyponatraemia from non-malignant causes.
(3) Patients with malignancy but where hyponatraemia is not delaying chemotherapy.
(4) Patients with volume depletion.
(5) Patients with hyponatraemia associated with significant neurological symptoms (e.g. coma, seizure).
(6) Patients with profound hyponatraemia (serum sodium <125 mmol/L) which may represent a medical emergency.
(7) Patients with mild hyponatraemia, without significant symptoms in whom the sole aim of treatment is normalising serum sodium concentration.

8. Proposed patient pathway

Fluid restriction is regarded as the first-line treatment for hyponatraemia secondary to SIADH, however success rates are limited due to poor patient compliance and slow onset of action. Cancer patients requiring chemotherapy need to be well hydrated therefore fluid restriction is not always an approporaite option. Second-line therapy for hyponatraemia is demeclocycline, although it is rarely used as it causes GI disturbance, renal toxicity and gives an unpredictable response with a slow onset of action.



9. Proposed governance arrangements

(1) Tolvaptan will only be available for inpatient use.

(2) Oncology services wishing to use tolvaptan will need authorisation from the locally designated endocrinologist.

10. Proposed mechanism for funding

Drug prescribing will be funded by NHSE via local specialised commissioning teams.

11. Proposed audit requirements

The following data will be available to commissioners upon request:
(1) Baseline pre-treatment data including; the specific indication for treatment, pre-treatment serum sodium concentration, biochemical response and number of days on tolvaptan.
(2) Adverse events, specifically over-correction of serum sodium.

An annual audit will be undertaken.

12. Documents which have informed this policy proposition

None

13. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016)