NHS England

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

Reference: NHS England: 16051/P

NHS England INFORMATION READER BOX		
Directorate		
Medical	Operations and Information	**Specialised Commissioning**
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference:	**05527s**
Document Purpose	Policy
Document Name	Tolvaptan for hyponatraemia secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in patients requiring cancer chemotherapy
Author	Specialised Commissioning Team
Publication Date	12 December 2016
Target Audience	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs
Additional Circulation List	
Description	Routinely Commissioned - NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	N/A
Superseded Docs (if applicable)	N/A
Action Required	N/A
Timing / Deadlines (if applicable)	**N/A**
Contact Details for further information	england.specialisedcommissioning@nhs.net

Document Status

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet.

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

First published: December 2016

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

Published by NHS England, in electronic format only.

Contents

Policy Statement

NHS England will commission tolvaptan for hyponatraemia secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in patients requiring cancer chemotherapy in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About hyponatraemia

Hyponatraemia is when there are low levels of salt (sodium) in the blood. This is a very common problem - it affects around 30% of patients in hospital.

- Mild hyponatraemia may have no symptoms and recover on its own.
- Severe hyponatraemia is known to be linked to increased death rates and prolonged stays in hospital.

Early signs of hyponatraemia include:

- headache

- feeling sick (nausea)
- being sick (vomiting)
- general feeling of being unwell (called ‘malaise’).

More advanced signs include:

- confusion
- agitation
- feeling drowsy.

In extreme cases there may be:

- fits (called ‘seizures’)
- difficulty breathing (called ‘respiratory depression’)
- becoming deeply unconscious (called ‘coma’)
- death.

Hyponatraemia must therefore be taken seriously and managed well.

An important cause of hyponatraemia is the Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Around 35% of hyponatraemic patients are affected by SIADH. There are various causes of SIADH - it leads to over-dilution of the blood and result low sodium levels.

About the current treatment

In most cases, hyponatraemia can be treated well enough by reducing the patient’s intake of fluids (‘fluid restriction’). However, patients respond slowly and compliance varies.

About the new treatment

Tolvaptan is a medicine taken by mouth.

- It works by blocking the action of a hormone.
- This reduces the amount of water re-absorbed by the kidneys - which improves sodium levels.

Tolvaptan is only licenced for use in patients with mild or moderate hyponatraemia.

Tolvaptan may have a role in some patients who have cancer and need chemotherapy. Chemotherapy is a type of medicine for cancer. It requires patients to be well hydrated. However, an increase in fluid intake can cause hyponatraemia.

This is dangerous because having low sodium levels can result in fits (seizures). In these patients, hyponatraemia may actually delay the start of chemotherapy - putting the patient at risk of further harm.

What we have decided

NHS England has carefully reviewed the evidence for use of tolvaptan. We have concluded that there is enough evidence to consider making the treatment available for patients:

- who have both mild to moderate hyponatraemia (caused by SIADH)

and

- have been delayed in starting chemotherapy due to their hyponatraemia.

1 Introduction

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

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 Antidiuretic hormone secretion (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, usually 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 (without significant neurological compromise) 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 will be commissioned, as stated, in patients with malignant disease, where chemotherapy is being delayed due to hyponatraemia.

Tolvaptan is an orally acting, selective vasopressin V2 receptor antagonist licensed for the treatment of hyponatraemia secondary to SIADH. It acts by blocking the binding of vasopressin to V2 receptors in the collecting duct of the kidney, reducing water reabsorption. The resulting aquaresis 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 license for tolvaptan states it is for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (EMEA/H/C/980). 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 (without significant neurological compromise), not severe or profound hyponatraemia.

2 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 biochemical changes may present with 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 the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (EMEA/H/C/980).

3 Aims and Objectives

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

The objective is to ensure evidence based commissioning with the aim of improving outcomes for patients with hyponatraemia secondary to SIADH who require cancer chemotherapy.

4 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 they see 500 new cases of lung cancer 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).

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of tolvaptan for hyponatraemia secondary to SIADH in patients with malignancy where chemotherapy is being delayed. The current evidence shows tolvaptan to be efficacious at increasing serum sodium concentration in patients with mild to moderate SIADH associated hyponatraemia (with no impairment of neurological state). There is also evidence relating to severe hyponatraemia however this was outside the scope of the evidence review.

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), 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. In addition, a US cost-effectiveness study by Dasta et al. (2012) 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, 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.

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.

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 studies with head-to-head comparisons of tolvaptan against fluid restriction or demeclocycline in the management of hyponatraemia secondary to SIADH. There is some evidence that tolvaptan is effective in improving serum sodium levels in patients with persistent hyponatraemia despite 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

The literature search did not identify any studies evaluating the cost effectiveness of tolvaptan in any subsets of patients as defined in the research question. However, Dasta et al. (2012) evaluate the potential direct hospital cost savings associated with tolvaptan usage among patients with SIADH (using the data from 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).

Exceeding protocol-recommended correction limits for serum sodium concentration following tolvaptan treatment in a sub-group of patients was reported in Verbalis et al. (2011). Out 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 baseline hyponatraemia (serum [Na+] <130mmol/L).

Tzoulis et al. (2015) reported 18% (10/61) with 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. Verbalis et al. (2011) reported that these adverse events were relatively similar between the treatment and control 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, 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 summary, the evidence indicates that in the short-term treatment with tolvaptan is usually well-tolerated.

6 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); 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).

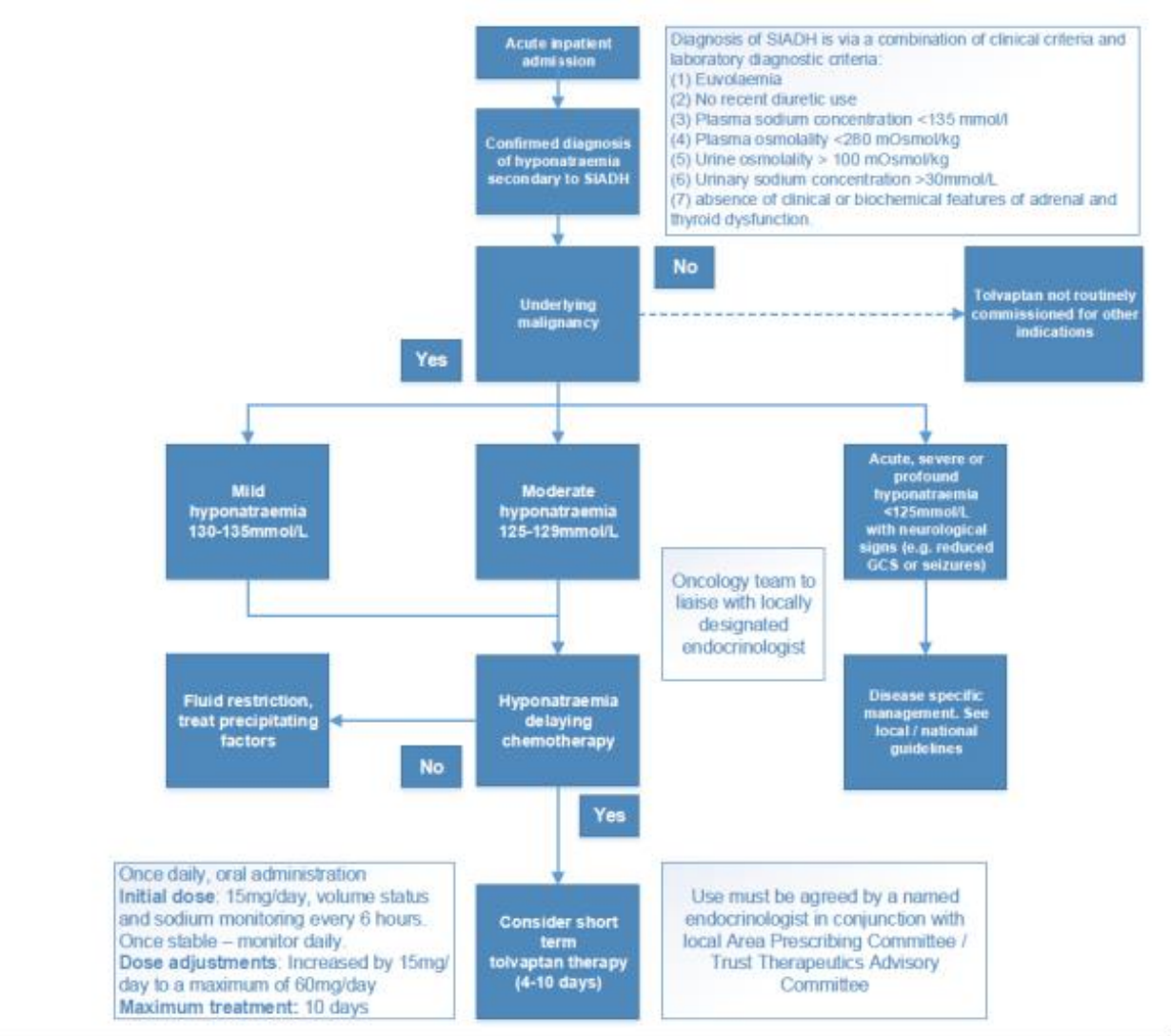
Tolvaptan will not be routinely commissioned by NHS England for:

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.

7 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 appropriate 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.



8 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.

9 Mechanism for Funding

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

11 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

None.

13 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

Chen, Shi; Zhao, Jia-Jun; Tong, Nan-Wei; Guo, Xiao-Hui; Qiu, Ming-Cai; Yang, Gang-Yi; Liu, Zhi-Min; Ma, Jian-Hua; Zhang, Zhen-Wen; Gu, Feng. Randomized, double blinded, placebo-controlled trial to evaluate the efficacy and safety of tolvaptan in Chinese patients with hyponatraemia caused by SIADH. J Clin Pharmacol 2014;54(12):1362-1367.

Dasta, Joseph F.; Chiong, Jun R.; Christian, Rudell; Lin, Jay. Evaluation of costs associated with tolvaptan-mediated hospital length of stay reduction among US patients with the syndrome of inappropriate antidiuretic hormone secretion, based on SALT-1 and SALT-2 trials. Hosp Pract (1995) 2012;40(1):41821.

Greenberg, Arthur; Verbalis, Joseph G.; Amin, Alpesh N.; Burst, Volker R.; Chiodo, Joseph A.; Chiong, Jun R.; Dasta, Joseph F.; Friend, Keith E.; Hauptman, Paul J.; Peri, Alessandro; Sigal, Samuel H.. Current treatment practice and outcomes. Report of the hyponatraemia registry. Kidney Int. 2015;88(1):167-177.

Hoorn, EJ; Lindenmas, J; Ziete, R Development of Severe hyponatremia in hospitalised patients: treatment related risk factors and inadequate management Nephrol Dial Transplant Jan 21(1) 70 – 76 (Pubmed). 2006

Upadhyay A., Jaber B.L., Madias N.E. (2006) Incidence and prevalence of hyponatremia. Am J Med 119: S30–S35

Vaghasiya, Rick P.; DeVita, Maria V.; Michelis, Michael F.. Serum and urine responses to the aquaretic agent tolvaptan in hospitalized hyponatremic patients. Int Urol Nephrol 2012;44(3):865-871.

Verbalis, Joseph G.; Adler, Suzanne; Schrier, Robert W.; Berl, Tomas; Zhao, Qiong; Czerwiec, Frank S.; SALT Investigators. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur. J. Endocrinol. 2011;164(5):725-732.

Tzoulis, Ploutarchos; Waung, Julian A.; Bagkeris, Emmanouil; Carr, Helen; Khoo, Bernard; Cohen, Mark; Bouloux, Pierre Marc. Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion. Clin. Endocrinol. (Oxf) 2015;0(0):0.