Author’s response to reviews

Title: Cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden

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Response to reviewers comments Manuscript title: Cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden

Reviewer #1: This paper is interesting and well written. However, I do not think that it is made sufficiently clear that the analysis is essentially entirely hypothetical. This should be made clear from the outset in the abstract - I had read as far as page 5 line 94 before I realised this. No real patients were involved, no real life cases were sequentially followed. Response: Discrete event analysis, feeding into a CUA, is a well-established method in cost-effectiveness modelling, especially for rare conditions when published data is scarce and access to real-world evidence is available to model the patient and treatment pathway. This kind of analysis if frequently used in reimbursement submissions to support decision making. We therefore feel that it is an accepted modelling convention, as used in other publications of similarly rare disease models, which suggests that the title is appropriate. The statistics are extremely complex and I would advise an independent statistical review which is not my area of expertise. The statistics section is far far longer than the results section which is inappropriate. The results are a little underwhelming given the huge volume of statistical work that was done. Page 3 line 41 - I would not regard HN < 125 as profound. Severe maybe, but not profound. See Gill et al, Clin Endo 2006.

Response: Amended accordingly. In summary - well written paper worthy of paper but independent statistical review needed. Reviewer #2: This is a simulation study with cost-utility analysis of tolvaptan versus no active treatment (NAT) in patients who failed to respond to fluid...
restriction or for whom the use of fluid restriction is not suitable from a Swedish societal perspective. The use of NAT as the alternative was explained. Based on various data sources and a few assumptions, discrete event simulation was developed to estimate costs and QALY’s. Most model parameters are reasonable. Some direct medical costs and costs related to lost productivity were considered. No in-direct and intangible costs were found. No cost discounting was performed in base case analysis; 3% discount rate was used in scenario analyses. The primary outcomes are costs and QALY’s in three subgroups. Some study limitations were addressed. Scenario analysis and univariate sensitivity analyses were performed. Key assumptions were not necessarily tested by sensitivity analysis. The conclusion was based on study results. Because this is a simulation study with synthesis of model parameters from different data resources, different model parameters may yield different results. It is important to clearly and explicitly explain the rationale of model parameter selections in the main body of manuscript. I was puzzled with my first reading of the main manuscript until I carefully review all supplementary data. Major revisions of the main manuscript are recommended to address the following concerns.

My comments on the main manuscript:

Line 1: The title seems incomplete. I recommend the title include CUA and indicate it is a simulation study. Response: CUA is the analysis that has been undertaken but the conclusion we are detailing is the cost effectiveness of the drug in SIADH. Accepted convention, as used in other publications of similar models suggests that the title is appropriate.

Line 46: (grammar) The most common cause of euvolaemic HN, is (please delete ,) Response: Amended

Line 63-64: (grammar) One sentence cannot be a paragraph. Please consider to combine with another paragraph. Response: Amended

Line 65: Please spell out EMA when it is first used. Response: Amended

Line 91: the phrase "56% of those were not provided a second therapy" is unclear. Is it out "of patients provided with fluid restriction as a first therapy" or out of "56% experienced a total increase of [Na+] of d"5 mEq/L"? Response: Amended

Line 93: The authors recognized NAT [is] "inappropriate in many cases where active alternative options exist". Please explain why this study did not select other active alternative options as comparators in addition to NAT. Response: The evidence on alternative treatment options is limited: We have double checked for alternative treatments and only found the following (from Greenberg 2013 and Greenberg 2015):

-A poster by Greenberg, 2013: Most people get NAT, some are treated with saline, 2.2% receive a vaptan, and 2.2% receive something else undefined.

-A publication by Greenberg, 2015: Until recently, treatment of hypervolemic HN has been limited to fluid restriction (FR) and correction of the underlying disorder. Treatment modalities for euvolemic HN have included FR, hypertonic saline (HS), loop diuretics, demeclocycline, and urea. With the approval of the vasopressin-receptor antagonists conivaptan and tolvaptan, more targeted treatment for euvolemic and hypervolemic HN became available. Although the above data show that some alternatives are used in clinical practice, there is no evidence base for urea, and very limited evidence for demeclocycline. Based on this evidence, as well as the fact that other vaptans are not approved in the EU and that demeclocycline is not available in Sweden, we did not select other active treatment options in the model. We have deleted where active alternative options exist, to avoid the impression that other alternatives exist.

Line 118-122: The rational of using the DES approach vs. a cohort model is provided. What is the optimization software or technique used to perform DES in this study? Response: The DES model was implemented in MS Excel using Visual Basic for Applications (VBA).

Line 161: why is Day 4 used? (It was explained in supplementary line 24-25 and line 127-133, but better to have a brief explanation here.) Response: An abbreviated explanation has been added in the manuscript body.