Reviewer's report

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

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Reviewer: Jun-Yen Yeh

Reviewer's report:

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 QALYs. 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 QALYs 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. Line 46: (grammar) The most common cause of euvolaemic HN, is (please delete,) Line 63-64: (grammar) One sentence cannot be a paragraph. Please consider to combine with another paragraph. Line 65: Please spell out EMA when it is first used. 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"? 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. 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? 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.) Line 162-165: Some direct medical costs and costs related to lost productivity were considered. No in-direct and intangible costs were found. The authors estimated 17% of study subjects had lost productivity due to the condition and assumed that every patient was discharged to home. For the rest of patients who did not work (i.e., 83%), some costs associated with societal burden may not be considered. This may under-estimate the societal costs. Line 178: Probabilistic sensitivity analysis is inherent in the DES model so I recommend you explicitly describe the inclusion of PSA. Line 190: In addition to costs and QALYs, please consider report comparative modeled outputs (i.e., hospital length of stay, readmissions and mortality) in the result
"increased incremental QALYs (0.0018 to 0.0028)" Is it clinical significant?- Line 195-198: I recommend results from selected scenario analysis be briefly summarized here; for example, results associated with key determinants. Line 216-222: These pieces of info are already included in the background section (line 71-77) so it is redundancy. I recommend at least one of these parts should be modified. Line 224-228: The patient population in this study is different from those in SALT I & II trials. This is an important limitation. Your statement, "our choice was based on Swedish guidelines for HN" is not clear. Please explain how it addresses this limitation. Line 260-262 should be linked to line 276-280. Line 271-272: I highly recommend that you briefly explain why "the effect on incremental cost-effectiveness is likely to be minimal" here in discussion. I did not understand the rationale until I read the supplementary data file (line 185-189). Line 274-275: The statement, "data limitations could lead to some benefits being ignored," should be moved to the next paragraph (line 276-280) because it does not make sense following line 267-273. However, this statement is not necessary true. For example, line 263-266 listed negative consequences instead of benefits. Please consider proper modifications. Line 282-283: There is also a possible over-estimation of cost-effectiveness. Please consider modifications of wordings and remove "due to data limitations". Table 2, line 30-32, page 23: "Absolute change in simulated EQ-5D at Day 30 from SALT I & II" was used for "Treatment-specific change in EQ-5D at Day 4". It seems over-estimate HRQL. The underlying condition may not be resolved at Day 4. Actual HRQL at Day 4 would be lower than HRQL at Day 30. As indicated in supplementary line 180-181, HRQL is associated with resolution of underlying conditions. HRQL at Day 30 was not necessary attributed to use of tolvaptan. Additionally, those with failed response to the initial treatment may have a lower HRQL than those found in SALT I & II. It may lead to over-estimate HRQL in your simulation. Please address these concerns. There are several assumptions in this study (in supplementary line 306-338; 1.2.1 Overview of assumptions). Please explain how you address uncertainty of these assumptions in the main manuscript or in the supplementary data file. Line 465-468: In figure 2, the brand name "Samsca" is used. Please change it to the generic name. Please change "SEK 1.2m" to "SEK 1.2 million". Please consider explain the parameter names in Figure 2. For example, it is not clear what "Discontinuation: lognormal- \ln \_sig" means to readers. My comments on the supplementary data file:Line 34-40: I disagree with this approach because there is a potential risk of data manipulation. HN Registry contains real-world data, which should be used to reflect "effectiveness". Is it better to address "effectiveness" rather than "efficacy" given the "cost-effectiveness" title? Line 50: This limitation is not listed in the main manuscript Line 53-56: Based on supplementary Table 2, OR= 7.549 (95% CI 3.881-14.682) which is smaller than the value used in Line 42 [11.5 (95% CI: 4.2-32.1)]. Should 7.549 be used instead of 11.5, the clinical benefits of using tolvaptan may be over-estimated in base-case analysis in the manuscript. As mentioned in Line 224-228 of the main manuscript, the patient population in SALT I & II were different from the study population. Therefore, use of 11.5 instead of 7.549 may be problematic. Line 107-108: which part of sensitivity analysis addresses the limitations? Line 109: The tolvaptan Post-Authorisation Safety Study (PASS) was not mentioned as one of the data sources in the main manuscript. Line 167: In supplementary Table 6, the distribution of LOS seems skewed. In addition, "there were differences in LOS depending on baseline [Na+]" (line 171-172). Please explain whether the simulation model considered the distribution of LOS and its relation with baseline [Na+]. Line 272: should be 135 mmol/L. Fig 7: brand name was used, please change it to the generic name. Line 363-364: The tolvaptan EQ-5D utility benefit at Day 30 was 0.0980 (Table 11). Line 380-382: "Baseline utility scores are estimated in these populations by subtracting the tolvaptan effect observed in Table 11
from literature sources [44, 45] to provide an approximate estimate for each population 'with HN'."
Please explain the rationale of subtraction. Line 389: is 3% discounting rate used here? Line 391-392: In reality, costs per bed day may decrease over time (for example, highest costs in the first 1-3 days). Was the average cost per bed day used or a function over time? Line 400: "In practice, these costs were very similar," but in Table 12, these numbers look different. Please explain the similarity. Line 486: Table 19 Please explain discounting in life-year. Is 3% discounting rate used here? Line 503-513: should be briefly summarized in the result section of the main manuscript. Line 505: please explain the need of this assumption. Page 43: Endnote is truncated.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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