NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Tolvaptan for treating autosomal dominant polycystic kidney disease [ID 652]

Dear Gethin

The Evidence Review Group, Kleijnen Reviews Ltd., and the technical team at NICE have now had an opportunity to take a look at the submission received on the 7 January 2015 by Otsuka Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 6 February 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Boglarka Mikudina, Technical Lead (Boglarka.Mikudina@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Encl. checklist for in confidence information

Section A: Literature searching

A1. **Priority Question:** Please justify the rationale behind limiting all literature searches to 2004 onwards and English language only.

A2. **Priority Question**: Please clarify why different search terms were used for the cost facet for the autosomal dominant polycystic kidney disease (ADPKD) and end-stage renal disease (ESRD) searches (Section 7.5.3 Resource Identification, appendix 10.13).

A3. Please provide the search terms and details of resources used for congress abstract searches (appendix 10.2.5).

A4. Please provide the search terms used for, and results found from Cost Effectiveness Analysis (CEA) registry searches (appendix 10.2.5).

A5. In section 7.4.5 Health Related Quality of Life (HRQoL) Studies (appendix 10.12.5): Please clarify what 'Internet' searches were conducted, providing details of sources used, search terms and results found.

A6. In section 7.5.3 Resource Identification (appendix 10.13): What search dates were used for the ESRD searches? A range of January – August 2014 is given in the company's submission (CS) for all databases. Please provide specific dates for each database searched.

Section B: Clarification on effectiveness data

B1. **Priority Question:** The primary endpoint in the main study (TEMPO 3:4) included in the section on clinical effectiveness was change in total kidney volume (TKV). However, TKV was not listed as an outcome of interest in the final scope. Please justify the use of TKV as the primary outcome in the submission.

B2. **Priority Question:** Section 1.13 of the CS states that "Hepatotoxicity has been observed in some patients receiving tolvaptan for ADPKD, which was reversible following discontinuation. To mitigate this potential risk, monthly monitoring of liver function for the first 18 months, and every 3 months thereafter, will be required." Please provide a proposed treatment pathway for tolvaptan including monthly monitoring of the liver function and possible transplantation required.

B3. **Priority Question:** Tables B12 and B13 provide subgroup data by chronic kidney disease (CKD) stage for TKV and annualised rate of change in renal function respectively. Please provide similar subgroup data by CKD stage for all endpoints defined in the scope.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

B4. **Priority Question:** Stopping rules are not considered in the CS (although the final scope states that these should be considered if evidence allows).

- What is the predictive value of a lower-than-average one-year increase of TKV of tolvaptan users for TKV increase in the next 2 years, correcting for baseline TKV (Tempo 3:4 data)?
- What is the predictive value of a lower-than-average two-year increase of TKV of tolvaptan users for TKV increase in the next 3 years, correcting for baseline TKV (Tempo 4:4 extension trial data)?

B5. Please provide an overview of the reasons why 530 participants (figure B2 on page 93 of the CS) did not fulfil the inclusion criteria.

B6. Drug induced liver injury was one of the main reasons tolvaptan was not approved by the FDA for usage more than 30 days. However, tolvaptan is approved for the treatment of hyponatremia (in the USA) and volume overload in heart failure (in Japan).[1, 2]

- Please provide the post marketing surveillance data on drug induced liver injury for any other relevant tolvaptan trials, e.g. the EVEREST trial.
- Please provide the maximum frequency of drug induced liver injury reported in any of the tolvaptan trials or post marketing surveillances done in the past.
- What is the expected efficacy of this risk management program given post-marketing data on other potentially hepatotoxic drugs?

B7. The TEMPO 3:4 trial only includes patients between 18 to 50 years of age.[1] Please clarify whether the anticipated marketing authorisation will be for all adult patients, and not restricted to those between ages 18 and 50 (on treatment initiation).

B8. Section 1.12 states that “With respect to evidence of rapidly progressing disease, no objective criteria are defined in the licensed indication meaning this assessment will be more subjective according to specialist clinical judgement.” Please provide further reasoning to clarify why no objective definition of rapidly progressing disease was used while definitions are available, for example in NICE clinical guideline 182[3].

B9. Section 2.6 of CS states that “Despite the majority of patients having a family history of ADPKD, the condition is often diagnosed relatively late and as an incidental finding during investigation of disease symptoms.” However, in section 2.2 of the CS the estimated diagnosis rate was 90%, with diagnosed prevalence of 3.9/10,000 and total prevalence 4.3/10,000. Also, in section 2.6 of the CS, the undiagnosed prevalence was estimated to be 4.3/10,000.

- Please provide a definition for ‘undiagnosed ADPKD’.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

- Please provide the correct prevalence for 1) undiagnosed but diagnosable (positive according to Pei criteria[4]), 2) undiagnosable (Pei-negative but will definitively develop ADPKD), 3) diagnosed and 4) total.
- Please provide a definition of a renal cyst (e.g. minimum size).

Section C: Clarification on cost-effectiveness data

Stopping rule

C1. **Priority Question:** Please explore the use of stopping rules (in line with the response to question B4 above) in the economic evaluation. Please include the costs of any medical resources associated by applying the stopping rule, based on the data available regarding treatment response and tolerability.

Subgroup analyses

C2. **Priority Question:** Please perform subgroup analyses for the base case stratified by the rate of decline of renal function and by baseline total kidney volume ([redacted]), as per the final scope issued by NICE. If not considered appropriate to undertake these subgroup analyses, please provide an explanation.

Estimation of treatment effect

C3. **Priority Question:** In the economic evaluation the treatment effect seen in TEMPO 3:4 is directly applied to renal expected Glomerular filtration rate (eGFR). This is justified (CS page 158-159) by the idea that the correlation between eGFR and TKV as observed in patients receiving no treatment may misrepresent the relationship in tolvaptan patients. Please perform a scenario analysis for the base case ([redacted]) with the treatment effect directly applied to TKV (and not applied to eGFR).

Model code error

C4. **Priority Question:** The model code is not consistent with the company submission and/or information from the Excel sheet. For instance, in 'Private Sub Simulate_initialize()', a GAMMA distribution is used for some utility parameters while a BETA distribution is mentioned in Table B35 and in the Excel sheet. Moreover, the opposite is true for some cost parameters (that is, a BETA distribution is used while a GAMMA distribution is mentioned in Table B35 and in the Excel sheet). These inconsistencies were observed by the ERG for multiple parameters including:

- uCKD1
- uCKD2
- uCKD3
- uCKD4
- uCKD5
- cPAIN
- cExtraVisits1

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

- cExtraVisits2
- cExtraVisitsSubs
- cMonitor1
- cMonitor2
- cMonitorSubs

Please correct all inconsistencies between the model code, the Excel sheets and the submission document, and, if necessary, provide an updated model file. Please also provide updated results of all analyses in the submission document, if necessary.

Model transparency

C5. **Priority Question:** The Markov trace and simulation is mainly coded in the Macro modules. The input parameters are presented and named in the Excel worksheets and referred to in the Macros. However, the parameters are often redirected/renamed, sometimes multiple times, in the Macro code (for example "pPatientState(i)") and parameters are introduced in the macro without clear description (for example "Patient_state(i)"). This severely hampers the model transparency. Please complete the table below for all parameters that are used in the Macro code (including all parameters that are redirected to each other). As an example the table has been completed for "PatientState(1)", "Patient_state (2)", "probPAIN_C(1, 2)", "probPAIN_C(1, 3)" and "probPAIN_C(2, 2)".

Parameters table

Parameter name VBA code	Parameter name Excel sheet	Reference in Excel sheet	Value	Description	Source
probPAIN_C(1, 2)	pPAIN_Ctrl	Control!$E$59	0.07	Annual probability of serious kidney pain for CKD stage 1 (control arm)	TEMPO 3:4 trial
probPAIN_C(1, 3)	-	Control!$F$59	0.004	Standard error of annual probability of serious kidney pain for CKD stage 1 (control arm)	TEMPO 3:4 trial
probPAIN_C(2, 2)	-	Control!$E$60	0.07	Annual probability of serious kidney pain for CKD stage 2 (control arm)	TEMPO 3:4 trial
Patient_state(1)	-	-	-	If this parameter is 1, then the patient is on hospital haemodialysis	-

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Parameter name VBA code	Parameter name Excel sheet	Reference in Excel sheet	Value	Description	Source
Patient_state(2)	-	-	-	If this parameter is 1, then the patient is on satellite haemodialysis	-
…					

Adverse events HRQoL

C6. **Priority Question:** In the base-case analysis of the economic model it was assumed that "… adverse events associated with tolvaptan treatment do not affect HRQL" (page 205) and therefore no adverse events (AEs) (besides kidney pain) were incorporated in the model. However, tables B18 and B19 in section 6.9.2 of the submission show that the numbers and the percentages of patients with serious treatment-emergent AEs as well as the most common AEs and serious adverse events are quite different for tolvaptan compared with placebo. This gives a reason to believe that the effect of AEs on HRQoL associated with tolvaptan is different compared with placebo.

a. Please fully justify why treatment dependent AEs and related disutilities are not incorporated in the model.

b. Please provide a scenario analysis for the base case ([redacted]) incorporating treatment dependent AEs and related effects on HRQoL.

c. Please clarify the reference/source for the 0.05 value given in table B49 for the disutility with treatment and why this is different from the 0.0123 value mentioned on section 7.4.9, page 200. Please clarify and justify which of these two is used for the 'Disutility with treatment' scenario analysis.

Adverse event costs

C7. **Priority Question:** No adverse events, other than kidney pain, were explicitly modelled in terms of costs in the economic model. Yet it is stated that "All patients incur the same health state costs while in a given health state, regardless of whether they are currently receiving tolvaptan" (page 215, CS). Tables B18 and B19 in section 6.9.2 of the submission show that the numbers and the percentages of patients with serious treatment-emergent AEs as well as the most common AEs and serious adverse events are quite different for tolvaptan compared with placebo. Please fully justify why adverse event-related costs are not incorporated in the model. Please provide a scenario analysis for the base case where treatment dependent adverse events and related costs are incorporated in the model ([redacted]).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Impact of severe drug induced liver injury

C8. **Priority Question:** Hy's law is a prognostic indicator that the FDA follows to evaluate the potential for drug-induced severe liver injury and typically refers to significant elevations of liver enzymes with concomitantly elevated bilirubin where etiologies other than the drug have been ruled out. Finding two Hy's law cases is considered highly predictive that the drug has the potential to cause severe drug-induced liver injury (DILI) when given to a larger population.[5] In the pivotal trial 2 Hy's law cases were found. It is uncertain whether the proposed treatment pathway will prevent cases of Hy's law and DILI. Please provide a scenario analysis for the base case ([redacted]) where the costs and quality of life impact of the occurrence of DILI is explored.

Additional benefits not captured in the estimation of QALY gain

C9. Please clarify whether it is the company's belief that tolvaptan offers additional benefits that are not incorporated in the estimated QALYs. If so, please provide further details and supporting evidence.

Age-standardised mortality rate

C10. Table B39 states that mortality in ADPKD patients prior to CKD stage 5 is equal to mortality in the general population. No information was found on mortality for CKD stage 5.

a. Please clarify and justify how mortality for CKD stage 5 patients was incorporated in the model.
b. Please provide the methods and results of a scenario analysis for the base case using ADPKD-specific mortality risks.

Jacobi process

C11. To incorporate correlation between parameters in the probabilistic sensitivity analyses, a Jacobi process was used.

- Please justify why the Jacobi process was preferred above the more commonly used Cholesky decomposition for this purpose.
- Please provide the results of a scenario analyses for the base case that uses a Cholesky decomposition instead of a Jacobi process.

Treatment cost weighting

C12. In addition to a half-cycle correction, weighting is applied to treatment costs, to reflect the timing of treatment discontinuations.

a. Please clarify that this weighting is necessary in addition to the half-cycle correction that is applied.
b. Please provide updated results of the base case ([redacted]) excluding this weighting of treatment costs.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Time horizon

C13. The first 3 years change in TKV, eGFR and the relative reduction in eGFR decline (slope) are directly based on trial data. Afterwards, these parameters are extrapolated using regression functions (based on TEMPO 3:4 trial data). Please provide the results of scenario analyses for the base case which use a time horizon of 3 years (that is no extrapolation), 5 years, 10 years, 15 years, 20 years, and 25 years ([redacted]).

Health state costs

C14. Please provide a one-way sensitivity analysis for all health state related costs (for example using the 95% confidence interval).

Extrapolation of treatment effect

C15. It is assumed that the treatment effect is time independent and will last while patients are on treatment. This is however uncertain. Please explore different assumptions regarding the extrapolation of the treatment effect: please provide scenario analyses for the base case in which the treatment effect after 3 years (the trial duration) is set at 0%, 10%, and 50% of the treatment effect observed in the pivotal trial.

Internal validity

C16. Please clarify how the internal validity of the economic model was assessed.

Section D: Textual clarifications and additional points

D1. Figure B12 on page 122 of the CS is difficult to read and interpret. Please provide this figure after correcting the formatting, adjusting the colouring if necessary.

D2. The text in the following figures is difficult to read because of the small size. Please provide enlarged text. Figure A6, A7, B3, B4, B5, B6, B7, B8, B9, B10, B11.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

References

[1] Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012;367(25):2407-2418.

[2] U.S. Food and Drug Administration. *FDA Briefing Document. Cardiovascular and Renal Drug Advisory Committee Meeting. August 5, 2013 [Internet]*. Silver Spring, MD: U.S. Food and Drug Administration, 2013 [accessed 13.1.15]. 220p. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM363343.pdf

[3] National Institute for Health and Care Excellence. *Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. Clinical guideline No. 182 [Internet]*. London: National Institute for Health and Care Excellence, 2014 [accessed 21.1.15] Available from: https://www.nice.org.uk/guidance/cg182

[4] Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;20(1):205-12.

[5] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). *Guidance for industry drug-induced liver injury: premarketing clinical evaluation [Internet]*. Silver Spring, MD: U.S. Food and Drug Administration, 2009 [accessed 20.1.15]. 25p. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf