National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Tolvaptan for treating autosomal dominant polycystic kidney disease [ID652]

You are asked to check the ERG report from Kleijnen Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **16 March 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment
[redacted] First example on Page 13 and in several places throughout the report. In the following sentence: "[redacted] Further detail needs to be marked as commercial in confidence to de-identify this statement.	The word "[redacted]" should also be marked as commercial in confidence.	[redacted]

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment
Page 17, Section 2.2. The ERG report states: "On 5 August 2013 the Food and Drug Administration (FDA) did not approve tolvaptan for the treatment of ADPKD due to risk of liver injury…" This statement is factually inaccurate. According to the FDA's complete response	The text "due to risk of liver injury" should be removed.	It is factually inaccurate to state that tolvaptan was not approved by the FDA on the grounds of safety.

letter to Otsuka, their decision not to approve tolvaptan was on the grounds of efficacy not safety. The FDA requested that Otsuka undertake an additional confirmatory study testing the hypothesis that tolvaptan slows renal function. No further safety data were requested for the purposes of FDA approval.		

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment
Page 22: "…might be able to modify the cause of disease in early ADPKD."	Replace "cause" with "course".	Typographical error with potential for misinterpretation.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment
Page 45, ERG comment: Results of TEMPO 3:4 'are not generalisable to all ADPKD patients' because 530 patients were excluded because they did not meet the inclusion criteria. Subjects were recruited as per the inclusion/exclusion criteria for the study, primarily because the total renal size was not >750 mL (n=370) or because their eGFR was <60mL/min within 31 days of randomisation (n=119). The population who entered the trial are considered representative of the ADPKD patient who are suitable for tolvaptan therapy.	The text "are not generalisable to all ADPKD patients' because 530 patients were excluded because they did not meet the inclusion criteria" should be removed.	The trial does have relevance to UK clinical practice

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment
On page 76 it is incorrectly stated that the annual probability of significant kidney pain	It should be stated that pain was independent of treatment	It is important that the modelling assumptions

was independent of CKD stage and dependent on treatment. Pain was independent of treatment after CKD stage 4.	after CKD stage 4.	are made clear to the reader

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment
On page 84 it is stated that Ericson and colleagues included ADPKD specific mortality for patients in CKD stages 1-4. This is incorrect; Ericson and colleagues used CKD and not ADPKD specific estimates from Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296-305	The sentence “However, the cost-effectiveness study by Erickson and colleagues included ADPKD specific mortality” should be deleted	The statement is factually inaccurate.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment
Page 113, para 2. “During the scoping workshop, clinical experts commented that the UK has approximately 70,000 ADPKD patients……” However, this is inconsistent with the EMA orphan designation estimates. The UK population is 64.1 M, total prevalence for UK is 4.3 per 10000, so there are 27563 individuals of all ages with ADPKD. Adjusting for those aged 18 and over results in 21775 individuals with ADPKD.	The figure of 70,000 should be removed as it is anecdotal and contradicts evidence based estimates.	The error should be corrected to ensure clarity

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment
Page 113, para 1. The statement “The potential effects on liver-enzyme levels and plasma levels of sodium and uric acid require monitoring” is incorrect. Sodium and uric acid would be monitored only based on symptoms.	The text should read “The potential effects on liver-enzyme levels require monitoring”	The error should be corrected to ensure clarity

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment

Page 113: “Therefore, the trial is not representative of UK practice.” This definitive statement cannot be substantiated and should be modified.	The ERG should re-word this sentence to rather reflect that there is some uncertainty regarding the generalisability of TEMPO 3:4 to the UK.	The ERG points to potential issues regarding the generalisability of the TEMPO 3:4 study in several places throughout the document. However the ERG does not acknowledge that ADPKD, being a genetic disease with no currently available disease-modifying treatment, also has many characteristics that do not change across country borders. These factors are in favour of the generalisability of TEMPO 3:4. Another comment regarding the trial not being representative of UK practice relates to the ERG considering that ADPKD patients are managed by primary care in the UK, but the trial was conducted in secondary care. This is not correct. ADPKD patients are not actively managed for their condition by their primary care physician. They may present to their primary care physician with related or unrelated complaints, but if they have been seen by a nephrologist then they remain under their care for their ADPKD. In light of these factors, we believe the ERG are mistaken to state definitively that the trial is not representative of UK practice

(please cut and paste further tables as necessary)