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29 September 2015

Royal College of Pathologists
21 Prescot Street
London
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By email to: [redacted]

Dear colleagues,

Re: Final Appraisal Determination – Tolvaptan for treating autosomal dominant polycystic kidney disease [ID652]

Thank you for lodging the appeal against the above Final Appraisal Determination. I am a non-executive Director of NICE and am deputising for Dr Helliwell as she is currently away.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). An appeal against a TA recommendation may be brought by "a person aggrieved by a recommendation." The RCPath were a consultee to this guidance which is a necessary (though not sufficient) factor in meeting this requirement. Since this is an Appeal against guidance, it is necessary to explain in what way the points raised in the Appeal may impact on the FAD. The Appeal letter does not do this. Thus I am assuming at this stage that the RCPath considers that that the Appraisal Committee (henceforth the Committee) may have reached an alternative conclusion in the FAD had it taken a different judgement on the issues in the Appeal points, but for reasons given below if the Appeal were to proceed it would be necessary for you to explain why that might be so.

The permitted grounds of appeal are:

- 1(a) NICE has failed to act fairly,[1] or

[1] Formerly ground 1

- 1(b) NICE has exceeded powers;[2]
- (2) the recommendation is unreasonable in the light of the evidence submitted to NICE

You have appealed on Ground 2. This letter sets out my initial view of the points of appeal you have raised: principally whether they meet the requirements for permitted grounds, and whether further clarification is required on any point. I note that you are happy to proceed with a written appeal. In this initial scrutiny of the Appeals process, the judgement to be made is whether the appeal points are (1) within scope and (2) arguable. You will have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

2.1 The Appraisal Committee has continued to assume that there is equal kidney pain in both groups on the basis that kidney pain is a symptom of chronic kidney disease, despite acknowledging that clinical experts indicate that kidney pain is not necessarily a reflection of chronic kidney disease. The ERG use a reference by Pham PC et al Clin Nephrol 2010: (reference 9 in the ERGs critique of the companies additional evidence) to support this, however this reference is an assessment of all types of pain, not just kidney pain. The predominant type of pain is musculoskeletal, with kidney pain relatively uncommon, so this reference is not supportive. Kidney pain related to ADPKD can be severe enough to require surgical removal of the kidney(s).

In the Company's model, (3.14), the probability of clinically significant pain was derived from the TEMPO 3:4 study, and applied to CKD stages 1 to 4. For patients who stopped tolvaptan, the probability of clinically significant pain reported in the control arm was applied. The ERG took a different view. (3.56) "*Equal kidney pain probability for both tolvaptan and placebo"* (company assumed probabilities of 0.05 and 0.07 respectively; see section 3.48)."

As stated in the FAD, 4.12, "....*The Committee understood that there were several differences in the assumptions adopted by the company in its additional evidence submission compared with those preferred by the ERG in its critique of the company's additional evidence, including assumptions relating to: treatment-related utility decrement for tolvaptan; probability of kidney pain for tolvaptan and placebo;...." . "The Committee discussed each of these in turn"*

After consideration of many points, and seemingly not influenced decisively by the reference 9 (Pham PC et al Clin Nephrol 2010), the Committee concluded (4.14) "...*that the conservative approach incorporating an equal kidney pain probability for both arms was*

[2] Formerly ground 3

appropriate for the base case..." and (4.13).."*that the true utility value decrement as a result of tolvaptan treatment [including possible pain reduction] was unknown, but that it was likely to be less than 0.0123 and may diminish over time* " Thus the Committee took an independent view from the ERG about the impact of tolvaptan having weighed the evidence presented.

Initial View. - I am minded to agree that the appeal point is within scope but that it is not arguable that the Committee did not discuss and weigh relevant considerations or that it arrived at a conclusion that was unreasonable.

This judgement does not imply that other conclusions might not have been both possible and reasonable. The Appeal purpose is not to reconcile a range of reasonable conclusions.
If you consider that (i) the conclusion drawn by the Committee could not **reasonably** be drawn from the range of evidence, AND (ii) that this impacted or at least could have impacted the FAD conclusion, then please elaborate.

2.2 The worst case scenario used by the ERG for drug induced liver failure requiring transplantation, with 0% survival is unrealistic based on liver transplant survival rates. The company has provided evidence of a more likely lower percentage of cases developing drug induced liver injury and has provided the European survival data indicating that there is a 79% 1 year and 72% 5 year survival. The UK data is even better than this: NHSBT data shows that for super-urgent liver transplants (in which acute liver failure due to drugs will fall), the 90 day patient and graft survival rates are 91.5% and 88.7 respectively and the 1 year and 5 year patient survival rates are 85.1% and 81.2% respectively, this data is based on 2004-14, the numbers are further improved for more recent years eg 2011-14 with a 1year survival of 89.8%. (http://odt.nhs.uk/pdf/organ_specific_report_liver_2014.pdf).

The ERG's exploratory analysis. (3.34) which adopted a worst-case scenario *.."assuming that all Hy's law cases would need a liver transplant at the end of year 1 and would die immediately after"* and which resulted in the ICER increasing from the company's base-case ICER of £34,733 to £35,751 per QALY gained (with the patient access scheme), was considered by the Committee (4.16)..".*The Committee considered whether it was appropriate to model the Hy's law cases, noting comments from the ERG that the possibility of future Hy's law cases cannot be eliminated. However, the Committee was mindful of its previous conclusion that the possibility of such adverse effects could be reduced by increased monitoring, The Committee also understood that liver biochemistry monitoring was relatively infrequent in the TEMPO studies, and that more frequent monitoring would be expected in clinical practice, which would further lower the risk of liver failure. The Committee concluded that the ERG base case reflected a 'worst-case' scenario and with the additional monitoring measures in place it was reasonable not to include Hy's law cases in the base* case."

The Committee went on to conclude that the ICER presented by the ERG (4.17) "*was likely to have overestimated the most plausible ICER for 3 reasons: (including) - the incorporation of Hy's law, which it estimated had increased the ICER by at least £2500 per QALY gained.*"

Initial View - I am minded to hold that the appeal point is not within scope as a valid appeal is an appeal against guidance: as the committee has rejected the impugned ERG scenario, it seems likely that the ERG scenario cannot have directed the guidance.

You may wish to elaborate on your point further if you consider the FAD recommendation might have been impacted by further consideration.

2.3 From the patients comments it is apparent that the thirst / requirement to drink large amounts of water, which has been taken to be a negative side effect by the ERG, is seen by patients as a positive thing. This is not reflected in the modelling.

The Committee did hear the views of patients on the impact of thirst and the tolerance to this was expressed. This is relevant to the treatment related decrement of utility which was considered by the Committee.

(4.17) "*The Committee estimated that this ICER* [that offered by the ERG] *was likely to have overestimated the most plausible ICER for 3 reasons*. Including ": *the incorporation of a treatment-related utility decrement of 0.0123, which the Committee regarded as a worst-case scenario"* and *"...the Committee therefore considered the most plausible ICER for adults with ADPKD CKD stages 2 to 3 with rapidly progressing disease was likely to be most closely represented by that reflected in the company's revised base case of approximately £23,500 per QALY gained*."

On this basis the Committee made its recommendation.

Initial View - I am minded to agree that the appeal point is within scope but that it is not arguable the Committee must have come to a different recommendation by further consideration of the points raised.

You may wish to elaborate on this further if you consider the FAD recommendation might be impacted by further consideration.

Conclusion

At this stage I am not minded to forward this appeal for further consideration by an Appeal Panel. I will be happy to consider any further comment you may have on the appeal points before making a final decision. Any such comments should be received within 14 days of the date of this letter.

Were an appeal to be held I can confirm it would be conducted on paper.

Yours sincerely

[redacted]

Non-Executive Director

National Institute for Health and Care Excellence