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ACMO/JL

25 June 2015

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Dear colleagues

Re: NICE appraisal on Tolvaptan consultation document

Thank you for giving me the opportunity to comment. I wish to point to some inaccuracies in 3.20 and 3.23 referring to work done by the ERG.

3.20 It is true that standard care as currently practiced in the UK has not been defined and mirrors that for CKD. Consensus guidelines have not been published. The issue of aggresive blood pressure managament has been addressed in the HALT studies recently published in the NEJM (Schrier et al, NEJM 2014; Torres et al, NEJM 2014). In the first study (HALT A) which investigated patients with preserved kidney function (eGFR>60ml/min), the lower blood pressure group (<110/75) was associated with a slower increase in total kidney volume (TKV) compared to standard blood pressure control (p=0.05) but no change in eGFR slope was detectable. This data contrasts with that for tolvaptan where both improvements in TKV and eGFR were observed. I have summarised these comparisons in a recent review for the Lancet (Ong et al, Figure 3A). There is therefore no basis to recommend more aggressive blood pressure reduction beyond standard levels (<130/80).

The benefits of increasing fluid intake have not been rigorously tested and remain unproven. In the TEMPO3/4 study, all patients including the control group were encouraged to maintain adequate hydration (drinking at least 3-4L/d). This is likely to have reduced the true differential effect between controls and treated groups by suppressing vasopressin and could be reflected by the lower rate of %change in TKV (5.5%) in the placebo group compared to previous studies (6.8-11.8%). Increasing fluid intake is not part of current standard care.

3.23 In the TEMPO3/4 study, TKV was initially accepted by the FDA as a primary end-point and therefore the study was powered for this outcome. It is important to point out that changes in TKV from MRI scans were measured by sterology (gold standard), not by the ellipsoid method, which would not be accurate enough to detect changes in TKV and lack precision for measuring TKV.

With kind regards

Yours sincerely

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