IPSEN
Innovation for patient care

18th September 2008

Mr Mark Taylor
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Dear Mr Taylor

Thank you for your letter dated 4th September and for the opportunity to comment and elaborate on the appeal points.

We believe that Point 3 'The Institute has acted unfairly by effectively redefining the scope of the appraisal by focusing the review on gout flares rather than "management of hyperuricaemia" as outlined in the scope' remains a valid appeal point.

The rationale for this position is set out for this below:

In **FAD section 4.4** the NICE committee acknowledge both the evidence and logical argument for a clear link between sUA levels at or above 6 mg/100 ml and the presentation of gout symptoms, both flares and chronic non-flare events (renal impairment and reduction in tophi size etc).

'However, although it noted that there remained some uncertainty about the relationship between serum uric acid concentration and clinical benefits (such as gout flare control, renal impairment and reduction in tophi size and number), the Committee was persuaded that a reduction in the serum uric acid concentration below the 'saturation point' (approximately 6 mg/100 ml) was necessary to avoid precipitation of uric acid crystals in tissues in the long term. Additionally, although the association between serum uric acid concentration and symptoms of gout is complex and not completely understood, the Committee concluded that it was reasonable to assume that a relationship with symptoms is likely above a serum uric acid concentration of 6 mg/100 ml.'

In acknowledging and accepting this causal link, it appears unfair of the NICE review to not fully accept the inclusion of the quality of life impacts of chronic gout symptoms within the economic evaluation of febuxostat, with uncertainly in these utilities clearly acknowledged.

This position is further supported by **FAD section 4.5:**

'The Committee concluded that there remained some uncertainty about the relationship between absolute serum uric acid concentration and gout symptoms in general, and that this was an additional source of uncertainty in the estimation of the incremental QALYs gained.'

The issue here is not one of is there a link between sUA levels of above 6 mg/100 ml, but one of how to deal with potential uncertainty in this estimate.

The original submission and economic model supported this link using an EQ-5D based assessment of utility weights (preference weights) was used to link to alternative levels of sUA. This reflects and overall assessment of QoL impacts of gout (non limited to flares) and this is used in the model to present the benefit of achieving an sUA level below 6 mg/100 ml (as clearly directed in the BSR and EULAR guidelines.

From **FAD section 4.12:**

'The overall incremental QALY gain (0.032) included both the incremental QALY gain from the avoidance of gout flares and the 'chronic utility gain' from the prevention of gout-related symptoms. This is much higher than the overall incremental QALY gain (0.006) obtained from including the avoidance of gout flares alone.'

This in itself is absolutely consistent with the timing of the clinical events. Impacts of chronic health states (like tophi) will always be expected to be larger than short term acute events (even if the events themselves are very debilitating. Ignoring the chronic QALY gain will clearly raise the ICER value (i.e. 100% ignoring any link between sUA and utility) – but as per 4.4 and 4.5 the presence of this link is never in question (the magnitude of utility loss however is). Therefore, and credence to the £80,000 ICER should be limited – in fact this provides an upper limit to the ICER and not an alternative point estimate.

We have no further comments regarding the appeal point 4.

Yours sincerely