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Wyeth

Sent by email

[redacted]
Appeals Committee Chair
National Institute for Health and Clinical Excellence

02 June 2009

Dear [redacted]

Re:- Final Appraisal Determination – Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma

Thank you for your letter dated 19th May 2009, setting out your initial view of our points of appeal against the Final Appraisal Determination (FAD) for the above-mentioned technology appraisal. We acknowledge your acceptance of points 1.2 and 2.1, contained within our initial letter of appeal dated 12th May 2009, as valid grounds of appeal. We would like to make the following comments to elaborate on the points which you were minded not to refer to the Appeal Panel.

Ground 1: The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the *Institute's Guide to the Technology Appraisal Process*.

1.1 Inconsistent use of economic models in decision making

The Assessment Group and Wyeth economic models for this appraisal were developed in 2007/08, prior to and without regard to the introduction of the end-of-life supplementary guidance to Appraisal Committees in January 2009. Given their relative strengths and weaknesses with respect to construct and time horizon, one or other of the models could be considered to give the most plausible estimates of cost effectiveness depending on the scenario assessed and the decision criteria adopted.

Wyeth highlighted, during consultation on the original Appraisal Consultation Document (ACD) that due to the method of estimating the progression free survival (PFS) and overall survival (OS) of the various subgroups (according to histology and nephrectomy status) the duration of treatment with temsirolimus had been overestimated in the Assessment Group economic model of these subgroups. Wyeth proposed that the

estimates of PFS and OS of these subgroups be amended in the Assessment Group's model to better reflect the data observed in the pivotal clinical trial. This action would be consistent with amendments proposed for other technologies within this appraisal and our experience of the conduct of other multiple technology assessments.

Instead, and presumably in light of the fact that the Wyeth model gave similar, albeit slightly higher, base case estimates of the incremental cost effectiveness for the total population as the Assessment Group's model, the Appraisal Committee adopted the Wyeth model from which to derive the most plausible ICERs for treatment with temsirolimus. However it did so without taking into account the different time horizons of the Wyeth model (3 years) and the Assessment Group model (10 years). The time horizon of the model has a direct impact on the outputs. In the Wyeth model the ICER at 12 months is greater than the ICER at 24 months, with the ICER at 36 months being the lowest of the three. Similarly, the ICER in the Assessment Group economic model is much greater at 5 years than when calculated at 10 years for all drugs.

In the same way that it would have been inappropriate to appraise one drug at 10 years and another one at 5 years within the Assessment Group economic model, so Wyeth believes that appraising temsirolimus at 3 years and the rest of the drugs at 10 years, irrespective of the model used, is biased and inconsistent, and disadvantages all patients that could benefit from temsirolimus. In addition, since the two models are not identical as they are not perfect, the inconsistency of the use of models to make decisions introduces further bias in the appraisal.

The impact of the choice of model by the Appraisal Committee can be demonstrated in the application of the end-of-life supplementary guidance. However, the Appraisal Committee was presented with the parameters for cost and life years gained by temsirolimus, derived from the Wyeth model only.

It would therefore have been appropriate to also use the parameters derived from the Assessment Group model in the quantitative exploration of the additional weight that would need to be assigned to the original QALY benefits in the full patient group for the cost effectiveness of temsirolimus to fall within the current threshold range. Indeed section 3.1.2 of the Guide to Methods of Technology Appraisal highlights the need to identify all relevant evidence for assessment and appraisal.

In selecting parameters derived from the Wyeth model over the Assessment Group model, based on its more appropriate calculation of subgroup ICERs, Wyeth believe that the Appraisal Committee made an error of judgement and failed to satisfy itself that the assumptions used in the reference case economic modelling were the most plausible, objective and robust for inclusion in the quantitative exploration of end-of-life in the whole population (Section 2.3.2 - Appraising life-extending, end of life treatments, Supplementary Guidance). Particularly in light of the Appraisal Committees view that the subgroup trial data were not considered robust enough for consideration under end-of-life criteria.

The estimate of the magnitude of additional weight (max Q at £30,000 threshold) which would need to be assigned to the original QALY benefits in the temsirolimus patient group derived from the Wyeth model is higher than the estimate derived from the Assessment Group's model (2.65 vs 2.03)[1,2].

Thus Wyeth maintains that in failing to consider the end-of-life supplementary guidance utilising cost effectiveness estimates from the Assessment Group model the Appraisal Committee has failed to act both fairly and in accordance with the Institute's published procedures and request that this point of appeal be considered by the Appeal Panel.

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[1] Addendum to FAD issued to stakeholders (Renal Cell FAD.zip)

[2] See section 2.1 of Wyeth's initial letter of appeal (12-May-09)

1.3 Failure to consider the degree of clinical need

There is no reference within the FAD to the fact that the overall survival of the patient population eligible for treatment with temsirolimus is currently less than half that of the patients eligible for treatment with bevacizumab or sorafenib. The median overall survival for patients receiving interferon (IFN-α), the current standard of care within the UK, was 7.3, 19.8 and 14.7 months the studies of temsirolimus, bevacizumab and sorafenib studies respectively. In the absence of the recognition of this fact it would seem unlikely that the Appraisal Committee gave particular consideration to the greater value patients with shorter life expectancy place on the increased survival they experience compared with patients with a better prognosis from the outset.

Sections 6.2.6.10 and 11 of the methods guide refer to the need for the explicit reference to the particular features of the condition and population receiving the technology and state that reasoning for the Committee's decision will be explained, with reference to the factors that have been taken into account, in the 'Considerations' section of the guidance.

Section 6.1.4 for the methods guide identifies the need for clarity and transparency to ensure that readers understand how the Appraisal
Committee has come to its conclusions. Therefore, of particular importance is the 'Considerations' section of the guidance document, which summarises the various issues that have been debated and the rationale for the conclusions drawn.

Wyeth maintain that in failing to consider the greater value patients with poor prognosis place on improvements in overall survival the Institute has neither acted fairly nor acted in accordance with its published procedures and request that this point of appeal be considered by the Appeal Panel.

Yours sincerely,

p.p.

[redacted]
Medical Director