Health Technology Appraisal: bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma

Wyeth welcomes the decision by the Appraisal Committee to consider new data and conduct a further review of the evidence.

We are, however, disappointed that NICE has not specifically considered the issues raised by Wyeth in its previous response to the Assessment Report and the Appraisal Consultation Document (ACD) with regard to the estimates of the cost effectiveness of temsirolimus. Not least because temsirolimus remains the only technology evaluated in this appraisal to demonstrate a significant improvement in the overall survival of metastatic renal cell carcinoma patients compared to interferon-α, the current standard of care within the NHS. Furthermore temsirolimus is the only technology demonstrating efficacy in poor prognosis patients and those with non clear cell carcinoma.

Wyeth highlighted discrepancies between the PenTAG model inputs/outputs and the evidence from the temsirolimus Phase III trial resulting in concerns regarding the interpretation of the sub-group analyses. Whilst we aim to address these issues in our response pending review of the economic model used in the above appraisal, we believe that resolution of these issues is vital to achieving a fair and robust appraisal outcome for patients with poor prognosis metastatic renal cell carcinoma.

Additional analyses

Wyeth finds the preferred assumptions and the additional analyses requested by the Appraisal Committee appropriate. Wyeth agrees with the Appraisal Committee in the interpretation of the evidence in the late submission made by Pfizer, and the caution in using such evidence to make recommendations due to the biased method of post hoc selection of patients for analysis. The results of the post hoc analysis imply that second line treatment in patients who have progressed on sunitinib therapy reduces their overall survival which is implausible, at odds with the findings in patients receiving interferon-α in the same study and with the findings of other studies highlighted in Pfizer's response to the ACD (p14). Such analyses would have been misleading and of little relevance or value to real clinical practice.

Drug administration costs

There appears to be some confusion with respect to the drug administration costs applied to drugs in this appraisal and the new assumptions tested. In the PenTAG economic model, drug administration costs were applied to interferon, bevacizumab and temsirolimus. The source of the IV administration costs were the NHS Reference costs for 2006-2007 uplifted to 2008 costs. This approach was based on the new HRG4 codes that introduced granularity into the costing of chemotherapy delivery. As pointed out in our previous comments the cost of oral administration was overlooked by the model (assumed to be zero), while HRG4 code SB11Z "Deliver exclusively oral chemotherapy" had a mean cost of £179 per cycle (or £186 when uplifted to 2008 costs). **Wyeth requests that for consistency the cost of oral administration of chemotherapy should be included in the economic model.**

HRG4 is clearly an improvement to HRG3.5, but chemotherapy delivery still does not reflect the actual variations in the IV delivery of drugs in terms of the duration of infusion. This has been challenged by one of the manufacturers and was used to run the economic model with a different drug administration cost. Wyeth believes that such assumptions should be based on evidence and applied consistently across all other treatments in this and in any future NICE appraisals. In the absence of UK NHS tariffs that reflect the duration of chemotherapy infusion we identified examples from other countries:

- In Australia, the cost of a 1h infusion is $60.10 AUD and a 2 h infusion costs $90.45 AUD (Reference: Medicare Benefits Schedule)
- In the USA, Medicare costs in 2005 were $93.29 US for a 1h infusion and another $26.16 US for any additional hour.

The examples above demonstrate that additional duration of an infusion increases the costs only marginally and not at the rate tested in the additional analyses. **Wyeth requests that any adjustments made to the administration cost of bevacizumab should be applied at the same rate to the administration cost of temsirolimus based on the marginal difference in duration of infusion between the two drugs as defined in the corresponding SPCs**:

- Bevacizumab: "The **initial dose** should be delivered **over 90 minutes** as an intravenous infusion. If the first infusion is well tolerated, **the second infusion** may be administered **over 60 minutes**. If the 60-minute infusion is well tolerated, all **subsequent infusions may be administered over 30-minutes**."

- Temsirolimus:" The recommended dose of temsirolimus for advanced renal cell carcinoma administered intravenously is 25 mg infused over a **30 to 60-minute** period once weekly."

Appraising end of life medicines

Wyeth very much welcomes the proposed changes NICE has announced to its technology appraisal process in relation to medicines used to treat rarer conditions where their function is to extend survival at the end of life. In particular, Wyeth wishes to point out that temsirolimus meets all the proposed criteria for inclusion under these suggested appraisal measures.

1. *The patient population does not exceed 7,000 new patients per annum.* We estimate that about 390 patients per annum would be eligible for treatment with temsirolimus in England and Wales.

2. *The medicine is indicated for a terminal illness where the patient is not expected to live more than 24 months.* Temsirolimus is indicated for the treatment of patients with a diagnosis of a terminal illness; these poor prognosis patients, on average, are not expected to live for more than 24 months. The PenTAG model estimates an average of 1.07 life years (12.8 months) on patients treated with interferon-α, the current standard of care within the NHS (Table 47, page 165, Assessment Report). We note that the corresponding figure for patients with good/moderate prognosis included in the sunitinib study is 2.29 life years or 27.5 months (Table 2, page 39, Additional Consultation Document).

3. *There is a substantial average extension to life compared to current treatment.* The temsirolimus Phase III trial data demonstrated that median life expectancy was extended to 10.9 months for patient treated with temsirolimus compared to 7.3 months with standard interferon treatment. This represents a substantial (49%) statistically significant median increase in length of survival. We note that the overall extension to life in the final analysis of the sunitinib study did not reach statistical significance (26.4 months vs 21.8 months on sunitinib and interferon-α respectively, p=0.051).

In addition, there is a subgroup of patients with the less common non-clear cell histology type of renal cell cancer (RCC) who, although being included in the temsirolimus Phase III trial, so far have been excluded from trials of the other new treatments being appraised. In this context, the findings of the Phase III temsirolimus trial were even more compelling. Median overall survival of patients with non-clear cell histology advanced RCC in the temsirolimus arm was 8.9 months compared to 4.3 months in the interferon group.

It is important to note that this sub-group of patients has no alternative treatment option. As noted in the Assessment Group Report, none of the other three drugs in this appraisal have included patients with poor prognosis in their trials nor have they demonstrated a substantial average extension to life.

Appraisal of ultra-orphan drugs

As the number of patients eligible for treatment with temsirolimus in England & Wales each year is estimated to be fewer than 400 (i.e. less than 1 in 50,000), Wyeth believes that NICE should have a clear view on the appraisal criteria

of ultra-orphan drugs to inform the current appraisal and any future appraisals of ultra-orphan drugs referred to NICE as a consequence of The Cancer Reform Strategy.

In conclusion, Wyeth looks forward to an appraisal outcome that fully recognises the special end of life circumstances affecting patients with poor prognosis renal cell carcinoma. We are hopeful that the proposed changes to the appraisal criteria for end-of-life medicines announced by NICE will enable this group of patients to benefit accordingly.