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

Wyeth consider that there are equality related issues with regards to patients eligible for treatment with temsirolimus that need special consideration within this appraisal and as a consequence the provisional recommendations of the Appraisal Committee are not sound and do not constitute a suitable basis for the preparation of guidance to the NHS.

Failure to adequately address the very small number of patients eligible for treatment, and their degree of clinical need, when making judgements on the acceptability of temsirolimus, based on the incremental cost effectiveness ratio (ICER) and the application of the supplementary advice when appraising life-extending, end of life treatments has resulted in discrimination against advanced renal cell carcinoma patients (aRCC) with poor prognosis.

Temsirolimus remains the only technology evaluated in this appraisal to demonstrate a significant improvement in the overall survival of aRCC 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**.

Appraisal Committee's preliminary recommendations

Wyeth welcomes the proposed recommendation of one of the four drugs (sunitinib) for patients with a good performance status. However, as identified in the FAD, this treatment is not suitable aRCC patients with poor prognosis (at least 3 of 6 prognostic risk factors) due to lack of evidence of efficacy. Moreover, as the ACD currently stands these poor prognosis patients will be denied access to temsirolimus - the only available innovative treatment with proven clinical effectiveness.

Wyeth is disappointed and concerned that this group of aRCC patients with poor prognosis are being denied access to an effective treatment that has been proven to increase overall survival. Albeit a 'very small group of patients' (as described in paragraph 4.3.12 of the ACD) this recommendation fails patients which Wyeth feels is discriminatory. We estimate that only about 238 patients in England would be eligible for treatment with temsirolimus annually and the overall drug cost to the NHS would therefore be less than £4 million per year. In return, treatment with temsirolimus adds another 3.6 months to a life expectancy of about 7 months, compared to treatment with current standard of care, interferon-α – a 50% extension to life that is particularly invaluable both for patients and for their families when time is so limited by the extent of disease at diagnosis, prior to treatment.

A recent report on the assessment and appraisal of oncology medicines produced by the Office of Health Economics (OHE) Consulting and the University of York[1] identified "the potential divergence between the values of patients, who directly experience the health state, and of the general public, who have been asked to make choices over hypothetical heath states which they might find difficult to fully understand. Cancer patients' preferences may be driven by specific characteristics of the disease. If someone has been told that they only have six months to live, gaining an extra two months might be worth a lot more to them than would a two-month gain if they had five years to live (over and above any discounting arising from the timing of future health effects.) As currently calculated a QALY valuation of health effects would not reflect this".

The report further highlights: "From a resource allocation perspective, under the current approach all QALYs are deemed to be of equal social value. However, our literature review indicates that there is societal willingness to give priority to the worse-off (people suffering from more severe illness), even if this involves a sacrifice in aggregate health gains".

Median overall survival for patients on temsirolimus is 10.9 months:

[1] Assessment and appraisal of oncology medicines: does NICE's approach include all relevant elements? What can be learnt from international HTA experiences?
http://www.ohe.org/lib/liDownload/634/POI%20Executive%20Summary%20V2.pdf?CFID=1540936&CFTOKEN=55059206

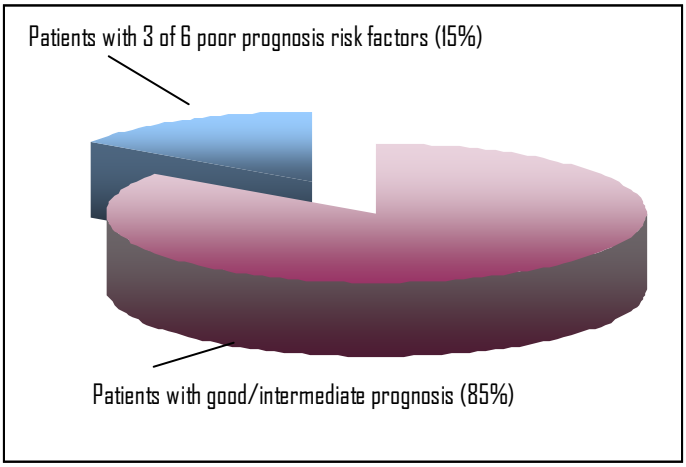
7.3 months median life expectancy with interferon-α	3.6 months life extension with temsirolimus (49%)

Median overall survival for patients on sunitinib is 26.4 months*:

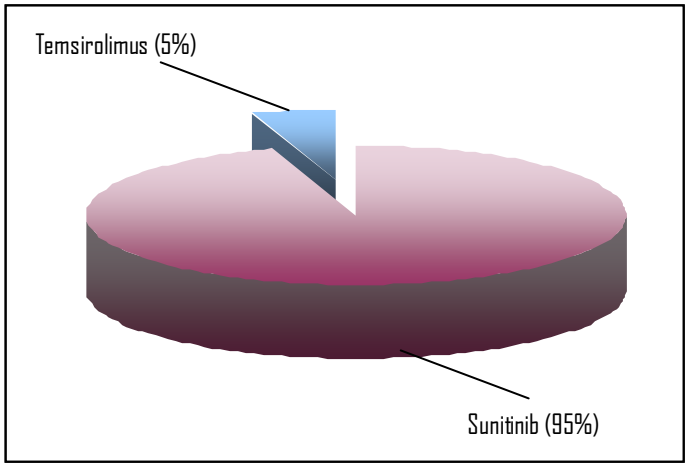
21.8 months median life expectancy with interferon-α	4.6 months life extension with sunitinib (21%)

** - Based on the final ITT population*

Patients eligible for treatment:
- Sunitinib: 1331 patients[2] in England could be treated with sunitinib (as recommended for use in FAD),
- Temsirolimus: 238 patients[3] in England could be treated with temsirolimus, **if recommended**.



Drug acquisition costs for these patients would be:
- Sunitinib 15 cycles cost £62.7mln (the 1st cycle is free), equivalent to 95% of all drug costs
- Temsirolimus 24 weeks treatment cost £3.4mln, equivalent to 5% of all drug costs



If both treatments were recommended for use, giving access to a first line treatment option for all aRCC patients in the UK, 15% of the patients with poor prognosis would incur only 5% of the total drug costs.

Evidence and interpretation

[2] NICE Costing template for Sunitinib (under consultation)
[3] See 'Wyeth submission to NICE", p. 51

In the Appraisal Consultation Document issued in February 2009, temsirolimus is described as having 'significant benefits compared with interferon- α in terms of overall survival, progression-free survival and tumour response rate' for aRCC patients with 3 of 6 prognostic factors indicating poor prognosis. Despite this recognition of the clinical effectiveness of temsirolimus, the ACD makes a negative preliminary recommendation based on the drug's cost effectiveness. The Appraisal Committee made this recommendation using the supplementary advice "Appraising life-extending, end of life treatments" issued in January 2009. The advice is an important step forward in the process of reviewing the decision rules currently adopted by NICE. However, as demonstrated by this ACD, there are still barriers that hinder patients' access to new beneficial treatments:

- The draft supplementary advice for consultation specified that it is not intended to cover ultra-orphan drugs, but this text has been excluded from the final version. Still, the final advice is not fit for use in the appraisal of ultra-orphan drugs and Wyeth believes that as a result the Appraisal Committee was disadvantaged in its decision-making process by being led to believe that 'small groups of patients' applies to ultra-orphan drugs including temsirolimus.

- The supplementary advice is very vague in its definition of the size of the population treated, and especially in the description, or rather lack of, the decision rules to be used by the Appraisal Committee in the appraisal – in particular, what constitutes an acceptable 'additional weight' thus making a treatment 'approvable', and what the weight would be should the medicine be ultra-orphan.

Appraising orphan and ultra-orphan drugs

The ultra-orphan nature of temsirolimus has been recognised by both NICE and the Department of Health[4]. On the basis that the majority of Citizens Council members thought that the NHS should consider paying premium prices for drugs to treat patients with very rare diseases, the draft second edition of NICE's Social Value Judgements document, detailing principles for the development of NICE guidance, stated that "NICE has not yet been asked to assess drugs for very rare conditions or diseases (which occur in fewer than 1 in 50,000 people in the population). If NICE was asked to do so, it would have to consider its approach". Wyeth believes that temsirolimus should be appraised using a separate set of appraisal criteria for ultra-orphan drugs due to the special circumstances they present, which has previously been acknowledged both by NICE and its Citizens Council.

Wyeth first raised these concerns when originally notified of NICE's intention to include Torisel in this appraisal and indicated that it would not be appropriate to appraise the drug through the Institute's existing process.

The only document issued by NICE on the appraisal of orphan and ultra-orphan drugs is available on the NICE website in its draft form that was submitted to the DoH in 2006.[5] The conclusions drawn in the document were based on the experience and the discussions NICE had had with clinicians, patients and patient groups and the Institute's Citizens' Council.

Orphan disease was defined as one with prevalence of less than 5 per 10,000 of the population. According to that document:

> *"The Institute does not consider, therefore, that any changes to its processes are needed for the appraisal of conventional "orphan drugs" with a prevalence of greater than 1 in 50,000. "*

In contrast, the ultra-orphan drugs have been described as follows:

> *"There would, however, be problems in the appraisal of drugs for very rare diseases – "ultra-orphan drugs" – largely because of their high costs. The Institute recommends that this group be defined as conditions with a UK prevalence of less that 1 in 50,000. NICE's advises the adoption of this definition for two reasons: first, it matches the prevalence criteria (less than 1000 persons in the UK) used by the National Specialist Commissioning Advisory Group in determining those conditions that should fall within its*

[4] In correspondence with Wyeth and in communications between NICE and DoH released to Wyeth under the FOI Act.
[5] Accessible from: http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf

programmes; and, second, it encompasses all products that appear, both now and in the foreseeable future, to be particularly problematic."…. Treatments for ultra-orphan conditions that present special difficulties are characterised by all of the following features:
• high acquisition costs and correspondingly high ICERs;
• use solely for an ultra-orphan disease (ie not also indicated for non-ultra-orphan diseases);
• use in ultra-orphan diseases that are chronic, severely disabling, and/or life-threatening; and
• potentially for life-long use;

In the same document NICE proposes that:

… separate decision rules (ie the range of ICERs considered "cost effective") will need to be developed and adopted for these products. […] based on the ICERs of those ultra-orphan drugs currently on the UK market. This will provide an implicit benchmark against which new ultra-orphan products can be evaluated. […] further work will be necessary to provide more robust data, and that a final position on cost effective ICERs will need to be confirmed through wider consultation. […] However, it appears that at current prices indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (ie a ten-fold increase on the decision rules currently applied in conventional appraisals).

Nevertheless, and despite this recognition, temsirolimus has still been appraised subject to NICE's standard cost-effectiveness threshold range and not surprisingly, it has failed to fall within the range of acceptability. **Furthermore, after applying the supplementary advice on "Appraising life-extending, end of life treatments", the group of aRCC patients with the poorest prognosis, the shortest life expectancy and the greatest clinical need were still denied this life-extending treatment.**

In conclusion

Wyeth believes that in the absence of a clear set of decision rules for the appraisal of ultra-orphan drugs, the Appraisal Committee should recommend temsirolimus for use within its ultra-orphan aRCC indication by allowing for a greater end-of-life premium due to its ultra-orphan features as described by NICE in the document cited above. This way, the difference between orphan and ultra-orphan drugs would be taken into account and the **very** small population of patients with poor prognosis aRCC would also benefit alongside the larger population with good/intermediate prognosis.

Other comments

Section No.	Section Title	Comments
3.1.3	The technologies - Bevacizumab	The duration of bevacizumab infusion should be included to be consistent with details provided for temsirolimus in section 3.4.3. – '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.'
4.1.15	Clinical effectiveness – Sorafenib	The term low MSKCC prognostic score is open to misinterpretation and is inconsistent with the other references to prognosis. Suggest using the term 'favourable' as in section 4.1.2 for example
4.1.23	Summary of clinical effectiveness	In contrast to the other technologies, there is no summary of the safety of bevacizumab despite the finding that more than twice the number of patients receiving the drug discontinued due to adverse events compared with IFN-α only (See section 4.16).
4.1.24	Summary of clinical effectiveness	To be consistent with section 4.1.19, this section should state that 'sorafenib was associated with significantly more adverse events…', rather than slightly.
4.2.18	Assessment group model	Please note, as previously communicated that to NICE in our comments on the PenTAG economic model, that the current list price for Torisel 30 mg vial is £620.