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Wyeth

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Mr C Feinmann
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Dear Mr Feinmann

Health Technology Appraisal "Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma"

Wyeth has reviewed the Appraisal Consultation Document (ACD) for the above appraisal and is extremely dismayed by its conclusion that Torisel (temsirolimus) should not be made available to patients with advanced renal cell carcinoma (aRCC) on the basis that it would not be a cost-effective use of NHS resources.

The conclusion of the ACD has been reached despite the unequivocal evidence demonstrating the clinical effectiveness of Torisel and the Appraisal Committee's own acknowledgement of the significant clinical benefits this drug has to offer patients with aRCC.

Wyeth believes that denying this group of patients access to the real and measurable benefits of Torisel in extending survival is unconscionable. It is a devastating and cruel blow to patients and their families.

It is Wyeth's opinion that this preliminary recommendation is fundamentally misguided on two counts:

- Firstly, as an ultra-orphan drug, Torisel, has been subject to an inappropriate appraisal methodology.
- Secondly, critical feedback submitted by Wyeth in response to NICE's earlier assessment report has largely been ignored.

As a consequence Wyeth **does not** consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

Inappropriate appraisal methodology

We remain extremely concerned that this appraisal has been carried out in the absence of any clear NICE framework for appraising ultra-orphan drugs and identifying what the appropriate decision rules should be.

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.

NICE itself has previously acknowledged that ultra-orphan drugs present special difficulties for appraisers and has highlighted the need to identify an appropriate appraisal methodology. The majority of the institute's Citizens Council members came to a conclusion that it is sometimes, or always, justified for the NHS to pay premium prices for ultra-orphan drugs[1]. To this end, NICE has even indicated that "at current prices, indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (i.e. a ten-fold increase on the decision rules currently applied in conventional appraisals)"[2]. Nevertheless, despite this recognition, temsirolimus has still been appraised subject to NICE's standard cost-effectiveness measures.

Yet, despite the lack of appropriate appraisal methodology, Torisel has remained in scope. Unsurprisingly, Torisel has failed to meet NICE standard cost-effectiveness threshold.

By applying its standard appraisal criteria, NICE has produced an ACD that, if implemented, will seriously disadvantage and discriminate against a small and vulnerable group of patients, i.e. aRCC patients with the poorest prognosis. Contrary to the spirit and aspirations of the NHS, NICE will have succeeded at denying a group of patients with the greatest clinical need potentially life-extending treatment.

The underlying fallacy of this approach is demonstrated by the fact that, as an ultra-orphan drug, temsirolimus would have a very limited impact on the overall NHS budget. Annually, approximately 390 patients with newly diagnosed poor prognosis aRCC in England and Wales are eligible for treatment at an additional £22,000 lifetime cost (from the PenTAG model). The total cost of providing all of these patients with Torisel treatment would thus amount to an additional £8.6 million per annum, which needs to be seen within the context of an annual NHS budget for England of over £100 billion per year[3]. However, not all patients would be suitable for such a treatment, thus the actual NHS spending could be considerably lower.

The total potential patient population for current and future indications for temsirolimus is anticipated to be less than 1,000 patients in the UK. Concessions within the regulatory approval process for orphan drugs adopted by government agencies are in recognition of the economic difficulties associated with the development of treatments for rare conditions. The failure to take into account such factors during health technology appraisal creates a disconnect between the development and utilisation of such products.

Data from subgroup analyses

Wyeth is also concerned that critical feedback we submitted in relation to the assessment report has not been dealt with appropriately and as a consequence the summary of the cost effectiveness of temsirolimus is not a reasonable interpretation of the evidence.

We are particularly concerned that issues relating to the interpretation of data from subgroup analyses have not been given sufficient attention and have only been addressed superficially. Furthermore, the results of the PenTAG cost-effectiveness analysis of temsirolimus in clear and non-clear cell RCC patients

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[1] NICE Citizens Council Report – Ultra Orphan Drugs. Available at: http://www.nice.org.uk/niceMedia/pdf/Citizens_Council_Ultraorphan.pdf
2 National Institute for Health and Clinical Excellence. Appraising Orphan Drugs. Available at: http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf; Accessed on 26 August 2008.
3 Department of Health. Departmental report 2008. The Stationery Office, London 2008.

demonstrated inherent errors, casting serious doubts over the robustness of their modelling approach across all populations analysed. Please see the Appendix for further details.

We believe that the Appraisal Committee should have been provided with the best available evidence. Instead, it appears that the Appraisal Committee relied on secondary data sources thus our original data have been compromised. As a result, the ICER for the temsirolimus treatment of aRCC patients with non-clear cell histology has been overestimated. This is especially disappointing since this subgroup of patients is especially disadvantaged as interferon is less effective in this subgroup compared to other patients with clear cell histology RCC. In particular, it should be noted that trials of other new treatments have excluded this subgroup of patients.

Moving ahead

It is Wyeth's view that NICE should be seeking to put in place appropriate methodologies to appraise ultra-orphan (and orphan) drugs on a fair and equitable basis. To that end, Wyeth would very much welcome the opportunity for Torisel to be used to test the integrity and robustness of any such methodologies NICE is considering for appraising ultra-orphan drugs. As a company, we would welcome the opportunity to work constructively with NICE to facilitate this process.

Yours sincerely

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Appendix

Wyeth UK has already submitted detailed comments on the Assessment Report. This example focuses on the ability of the different models to replicate the duration of therapy seen empirically in the clinical trial and the impact this has on the estimates of disease progression, overall costs and thus the ICERs generated.

In the subgroup analysis for patients with non-clear cell RCC, the PenTAG model predicts a duration of treatment on IFN of 4.6 months and on temsirolimus of 22 months (Table 1). In comparison to the observed empirical data from the Phase III study, the PenTAG model's predictions are an overestimation of the observed duration of treatment. In the IFN arm this overestimation is by a factor of 2.1 and in the temsirolimus arm the overestimation is by a factor of 3.6. Thus, though the PenTAG model is over estimating treatment duration in both arms it is doing so at a higher rate in the temsirolimus arm. In comparison, the Wyeth model predictions are more in line with the empirical data and the magnitude of the difference is similar in the two arms.

Table 1: Non-clear cell sub-group analysis: comparison of PenTAG and Wyeth model predictions of treatment duration.

	PenTAG model	Wyeth model	Phase III trial
Interferon			
Mean duration of treatment	**4.6 months**	2.99 months	**2.14 months**
Temsirolimus			
Mean duration of treatment	**22 months**	7.64 months	**6.12 months**

We ran the Wyeth model to analyse the base case using the same assumptions as the PenTAG analysis:

- IFN self-injection rates: 75% self-injecting;
- same drug unit costs;
- same drug administration costs.

Not surprisingly, the greater PenTAG estimates of treatment duration (Table 1) resulted in greater drug and drug administration costs – see Table 2. The IFN drug costs were 2.4 times greater than the Wyeth estimates, while the temsirolimus drug costs estimated by the PenTAG model were 3 times the corresponding cost prediction of the Wyeth model.

Table 2: Non-clear cell sub-group analysis: comparison of PenTAG and Wyeth model predictions of drug and drug administration costs.

	PenTAG model	Wyeth model[4]
Interferon		
Drug costs	£2,823	£1,163
Drug administration costs	£367	£161
Temsirolimus		
Drug costs	**£49,888**	£16,345
Drug administration costs	**£17,497**	£5,229

The base case ICER dropped from £133,848 to £80,681 for the non-clear cell sub-group in the Wyeth model. However, the overestimated treatment durations and costs of the PenTAG model resulted in an ICER which is higher than the base case analysis. (Table 3).

Table 3: Non-clear cell sub-group analysis: comparison of PenTAG and Wyeth model predictions of QALYs, total costs and ICER.

	PenTAG model	Wyeth model[4]
Interferon		
QALYs	0.53	0.29
Total costs	£6,519	£18,172
Temsirolimus		
QALYs	1.17	0.55
Total costs	£71,732	£39,155
ICER - base case (£/QALY)	£94,385	£133, 848
ICER - non-clear cell (£/QALY)	**£102,457**	**£80,681**

[4] The Wyeth model was run with PenTAG base case unit costs (drugs and drug administration costs) and the rate of 75% self-injection of IFN in order to allow for direct comparisons.

Wyeth has not been given access to an executable version of the PenTAG model and therefore is not in a position to ascertain the impact of the PenTAG estimated Weibull parameters as well as the other assumptions made on the disease progression and treatment duration being modelled. But it appears that for the non-clear cell sub-group the overall ICER might be much lower than the current PenTAG estimate of £102,457.

There are two important messages from this comparison:

1. The sub-group analysis illustrates that the PenTAG model appears to be flawed and the outputs are inaccurate. This could apply more widely than just to the example cited here. The PenTAG model should be revised and the updated results used to inform the recommendation in the FAD.

2. The current practice of providing non-executable models to manufacturers hinders the ability to comment fully on the appraisal process as it does not allow for testing the robustness of models.