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Wyeth

12 May 2009

[redacted]
Chief Executive
National Institute for Health and Clinical Excellence
Midcity Place
71 High Holborn
London WC1V 6NA

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 the Final Appraisal Determination (FAD) for the above –mentioned technology appraisal, which we received by email on 21st April 2009.

We hereby confirm that in accordance with the procedure set out in the email and the "Guidance for Appellants", Wyeth wishes to appeal the following aspects of the appraisal process and the resultant proposed guidance on the grounds of appeal, as set out below.

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 sought to apply a common modelling approach for all the technologies in the appraisal. It did this by defining progression free survival (PFS) and overall survival (OS) for the current standard of care - interferon (IFN) and applying treatment specific PFS and OS hazard ratios to model the benefit derived from each technology being appraised. Manufacturers produced economic models in isolation utilising a number of different approaches - Wyeth's model utilised patient level data from the pivotal phase 3 study.

For 3 of the 4 technologies, bevacizumab, sorafenib and sunitinib, the most plausible ICERs considered by the Appraisal Committee were derived by amending the Assessment Group's model in light of comments received from stakeholders during the course of the appraisal. This involved a significant amount of additional analysis undertaken by both the Assessment Group and the DSU. However, for temsirolimus rather than amend the Assessment Group's model in light of comments regarding the duration of temsirolimus treatment, the decision was taken to utilise the manufacturer's model.

Our concerns regarding the duration of temsirolimus treatment in the Assessment Group's model were with respect to the sub-group analyses (e.g. histology and nephrectomy status etc.) and arose as a consequence of applying sub-group specific PFS and OS hazard ratios to the IFN curve for the total population rather than to sub-group specific IFN curves. Wyeth's concerns do not extend to the analysis of the patient population as a whole as the method described above is appropriate for this group. Indeed

the Assessment Group demonstrated the closeness of fit of their model compared with the manufacturer's model to the empiric OS trial data (Assessment Report p125).

Section 3.1.2 of the Guide to Methods of Technology Appraisal highlights the need to identify all relevant evidence. Section 3.1.3 of the same Guide identifies that modelling should be methodologically sound and, in particular, minimise any bias. Section 5.1 states that the Institute seeks to promote high-quality analysis and to encourage consistency in analytical approaches.

It would therefore be appropriate for consistency of decision making with the other technologies in the appraisal, and to avoid bias, to use the Assessment Group's model when considering cost effectiveness and the application of the End of Life Supplementary Guidance to the appraisal of temsirolimus.

In failing to apply the End of Life Supplementary Guidance to the cost effectiveness estimates from the Assessment Group's model the Institute has failed to act both fairly and in accordance with its published procedures.

1.2 Failure to consider the size of the patient population

The FAD (Section 4.3.14) acknowledges that the patient population eligible for treatment with temsirolimus is very small. The sole indication for temsirolimus is for the treatment of a subgroup of advanced renal cell carcinoma patients i.e. those who have at least three of six prognostic factors. With an estimated 390 eligible patients in England and Wales this technology meets the criteria for an ultra-orphan drug which NICE has previously identified as presenting special difficulties for appraisal. This difficulty arises from the similar development costs for drugs to treat very rare conditions as for drugs for more prevalent conditions. Where there is a very small number of patients eligible for treatment, this can result in the economic necessity for a comparatively higher price per unit dose. Such drugs also provide the manufacturer with difficulties in proposing a patient access scheme whilst at the same time securing a return on investment.

The conclusions of the Institute's Citizens Council, in its report to the Institute on ultra-orphan drugs, and the judgment of the Institute's board, suggest that there is public support for the NHS to meet the reasonable treatment costs of expensive treatments for ultra-orphan conditions. This would accord with the NHS's egalitarian principles.

On this basis 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 welcomes the End of Life Supplementary Guidance, however whilst it addressed the value patients and society place on extension to life at the end of life, no additional consideration has been afforded to society's view that the NHS should be prepared to pay a higher price for drugs to treat patients with very rare life threatening diseases. Thus the Supplementary Guidance does not address the specific needs of ultra-orphan drug assessment.

Section 5.2.3.1 of the Guide to the Methods of Technology Appraisal states 'the requirements for evidence of effectiveness include the quantification of the effect of the technologies on the course of the disease, the effect of the technologies on patients' HRQL and the valuation of those effects in a manner that reflects the preferences of the general population'.

Further Section 6.2.5.5 of the same Guide states 'The Committee should also take into account advice from the Institute, which is partly informed by the work of its Citizens Council, on the appropriate approach to making scientific and social value judgements'.

Whilst Section 6.2.6.10 cites the need to make explicit reference to the 'particular features of the condition and population receiving the technology' when making judgements about the acceptability of a technology.

In section 4.3.14 of the FAD the Appraisal Committee having noted that the patient population is very small then cited the lack of direction from the Department of Health for not taking into account when reaching its determination regarding the use of temsirolimus for the treatment of renal cell carcinoma patients with poor prognosis.

However Section 6.2.6 of Methods Guide makes it clear that the existing directions from the Secretary of State for Health give Appraisal Committees discretion when determining cost effectiveness to take into account those factors it considers most appropriate to each appraisal. The factors listed include the degree of clinical need of the patients with the condition under consideration and the particular features of the condition and the population receiving the technology. Furthermore the Appraisal Committee does not use a fixed ICER threshold above which a technology would automatically be defined as not cost effective.

By not explicitly taking into account the very small size of the patient population when reaching its determination regarding the use of temsirolimus for the treatment of renal cell carcinoma patients with poor prognosis the Institute has neither acted fairly nor acted in accordance with its published procedures.

1.3 Failure to consider the degree of clinical need

Whilst section 4.3.1 of the FAD indicates that the Appraisal Committee considered the nature of advanced and/or metastatic renal cell carcinoma there is no evidence to suggest that it gave greater consideration to those patients with poor prognosis eligible for treatment with temsirolimus.

In its first report the Institute's Citizens Council identified severity of symptoms, impact on quality of life and length of life as features of disease which should be taken into account when considering clinical need. These features are affected to a greater degree in poor prognosis patients eligible for treatment with temsirolimus than in favourable or intermediate prognosis patients treated with the other technologies evaluated in this appraisal.

In its report on QALYs and Severity of Disease the Citizens' Council concluded that NICE and its advisory bodies should take the severity of a disease into account, alongside the cost and clinical effectiveness evidence, when making decisions.

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 identified that 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.) 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".

Section 6.2.6.8 of the Guide to the Methods of Technology Appraisal identifies the degree of clinical need of the patients with the condition under consideration as one of the factors the Appraisal Committee has been given discretion to take into account when determining cost effectiveness.
By not explicitly making a value judgement on the degree of clinical need when reaching its determination regarding the use of temsirolimus for the treatment of renal cell carcinoma patients with poor prognosis the Institute has neither acted fairly nor acted in accordance with its published procedures.

Ground 2: The Institute has prepared guidance which is perverse in the light of the evidence submitted.

2.1 Inconsistent use of economic models in decision making

Further to Appeal Point 1.1, Wyeth have estimated the impact of giving greater weight to QALYs and the magnitude of the additional weight that would need to be assigned for the cost effectiveness of temsirolimus to fall within the current threshold range (Table 1), based on the Assessment Group's model utilising the their estimates of temsirolimus administration costs and those accepted previously by the Appraisal Committee.

Table 1 – Impact of End of Life Supplementary Guidance – Temsirolimus[#]

Scenario	IC	I LYG	IQ original	ICER original	IQ max	ICER max	Original Q		max Q	
							£ 20,000	£ 30,000	£ 20,000	£ 30,000
Temsirolimus vs IFN, using PenTAG model and PenTAG administration costs (£197)	£22,272	0.450	0.236	£94,385	0.351	£63,453	4.72	3.15	3.18	**2.12**
Temsirolimus vs IFN, using PenTAG model with AC administration costs (£170)[†]	£21,420	0.450	0.236	£90,763	0.351	£61,026	4.54	3.03	3.05	**2.03**

Derived from data contained in the Assessment Report (p165) and the Addendum to the pre-meeting briefing: end of life - a quantitative exploration
[†] Appropriate NHS reference cost for a 1hr infusion proposed by the Appraisal Committee in TA162

We note that the additional weight (2.03 – 2.12) which would need to be assigned to the original QALY for the cost effectiveness of temsirolimus to fall within the current threshold range could be considered at the limit of what NICE regard as acceptable under the End of Life Supplementary Guidance.

In failing to consider the application of the End of Life Supplementary Guidance to the cost effectiveness estimates from the Assessment Group's model the Institute has prepared guidance which is perverse in the light of the evidence submitted.

Conclusion

Had the Appraisal Committee correctly identified the Assessment Group's economic model as providing the appropriate estimate of cost effectiveness upon which to apply the End of Life Supplementary Guidance, Wyeth believes that the additional weight that would need to be assigned to the original QALY benefits for the cost effectiveness of temsirolimus to fall within the current threshold range would be smaller. Furthermore had the Appraisal Committee given appropriate consideration to the degree of clinical need of the very small population of patients with poor prognosis advanced renal cell carcinoma Wyeth believes that the additional weight that would need to be assigned to the original QALY benefits for the cost effectiveness of temsirolimus to fall within the current threshold range would be smaller enough for temsirolimus to be considered as a cost-effective use of NHS resources. As the combined impact of the points raised has not been considered, the Appraisal Committee has failed in its duty and the Institute has prepared guidance

which is perverse in light of the evidence submitted. Consequently, Wyeth wishes to make an appeal based on the above-mentioned points.

Yours sincerely

p.p.

[redacted]
Medical Director

c.c. [redacted] – Project Manager