

Appeal by Derbyshire County Primary Care Trust relating to

NICE Final Appraisal Determination:

Ranibizumab and Pegaptanib for Age Related Macular Degeneration (March 2008)

- 1 This is an appeal to the National Institute for Health and Clinical Excellence Appeal Committee (the Institute) by Derbyshire County Primary Care Trust (the PCT). It is submitted following careful consideration of the Institute's published documents including:
 - 1.1 Final Appraisal Determination – Ranibizumab and Pegaptanib for age related macular degeneration (March 2008).
 - 1.2 Technology Appraisal Process: Guidance for Appellants (April 2004).
 - 1.3 Guide to the Technology Appraisal Process (April 2004).
 - 1.4 Guide to the Methods of Technology Appraisal (April 2004).

- 2 The PCT is aware of its responsibility and duties including:
 - 2.1 Improving the health and well-being of the population.
 - 2.2 Commissioning cost-effective and affordable comprehensive health care services for the population.
 - 2.3 Providing health care services.

- 3 It makes this appeal in order to bring to the attention of the Appeal Panel the absence of a properly arguable case for the treatment of age related macular degeneration with Ranibizumab in the Final Appraisal Determination (FAD), and in the knowledge that if NICE publish this Guidance it will lead to a demand for this treatment which will reduce the ability of the PCT to meet other medical and health needs.

- 4 The PCT wishes to appeal on the following grounds:
- a. Ground 1: That the Institute has failed to act fairly and in accordance with its published procedures.
 - b. Ground 2: That the Institute has prepared a FAD that is perverse in light of the evidence submitted.
 - c. Ground 3: The Institute exceeded its powers.

Ground 1 The Institute has failed to act fairly and in accordance with its published procedures

- 5 The Institute sets out in its document entitled *Guide to the Technology Appraisal Process* the role of consultees. Consultees can participate in consultation on the draft scope, the Assessment Report and the Appraisal Consultation Document. Throughout the process various documents are released to consultees. Paragraphs 3.3.1, 4.1.2, 4.1.3, 4.2.7, 4.4.1.10, 4.4.2.1 , 4.4.2.3, 4.5.2.3 4.5.2.6, 4.5.2.7 and Boxes 4.1, 4.3 refer to the various stages of consultation.
- 6 Further descriptions of the consultation are set out in the *Guide to the Methods of Technology Appraisal* and Paragraph 6.1.3 states that it is crucial that the views of consultees in the appraisal are taken into account.
- 7 The Institute will appreciate that PCTs reconfigured in October 2006. As a result of this PCTs merged and there were changes of personnel. High Peak and Dale PCT became part of Derbyshire County PCT on 1 October 2006. The successor PCT only became aware of the fact that it had a consultee role in September 2007. As a result of this there was not full consultation with the successor organisation to High Peak and Dale PCT. The PCT are unclear as to how the Institute sought to consult following the reconfiguration but is of the view that the Institute failed to properly and fully consult with a key consultee.

8 The PCT submitted comments on 24th October 2007. However by this stage some a key consultation stage had passed: the PCT did not have an opportunity to comment on the first Appraisal Consultation Document

Ground 2: That the Institute has prepared a FAD that is perverse in light of the evidence submitted.

9 Paragraph 4.3.2.1 of Technology Appraisal Process : Guide for Appellants states that to be perverse means obviously and unarguably wrong, to be in defiance of logic or so absurd that no reasonable Appraisal Committee could have reached such conclusions.

10 FAD paragraph 1.1 (Guidance) states:

“Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:

- *all of the following circumstances apply in the eye to be treated:*
 - *the best-corrected visual acuity is between 6/12 and **6/96**”*

FAD paragraph 4.3.25 then states that:

“The Committee also concluded that because the population in the clinical evidence base had a corrected visual acuity of 6/12 to 6/96, it would be appropriate for treatment with ranibizumab to be recommended within this visual acuity range.”

However paragraph 4.3.24 states that:

“ The Committee further considered that there could be differential gains from pegaptanib for different sub groups of patients according to their starting visual acuity The committee considered the position of the different sub groups with reference to cost effectiveness.....

11 Only in studies in which there are identifiable sub-groups can differential outcomes, and thus cost effectiveness, be determined. To therefore state that because such a subgroup were in the studies constitutes reason for agreeing to treat them represents a logical absurdity: NICE could on that reasoning never consider sub-group analysis

- 12 It is inconsistent with other Technology Appraisals which have considered sub-group analysis such as the recent TA135 which recommended that pemetrexed should only be used to treat patients with a WHO performance status of 0 or 1 even though patients with WHO performance status 2 were included in the trial.
- 13 The Institute had been presented with data in its Assessment Report (Table 4.19) showing that utilities varied considerably between visual acuity subgroups:

Table 4.19 Health state utilities used in economic model

Visual acuity range	Mean Utility	Standard deviation	95% CI
>6/12	0.89	0.16	(0.82 – 0.96)
6/12 to 6/24	0.81	0.20	(0.73 – 0.89)
6/24 to 6/60	0.57	0.17	(0.47 – 0.67)
6/60 to 3/60	0.52	0.24	(0.38 – 0.66)
<3/60	0.40	0.12	(0.29 – 0.50)

This data demonstrates that the loss of utility when vision deteriorates from 6/60 to 3/60 is just 0.05 and thus the loss from 6/60 to 6/96 must be even smaller and a small percentage of the overall loss of utility. The impact on cost effectiveness for this subgroup is considerable.

- 14 At Paragraph 4.3.7 the FAD states that “ *the Committee considered whether the clinical effectiveness of the anti VEGFs varies between subgroups defined according to baseline visual acuity. It noted that in the Assessment Group’s model treatment effect and rate of deterioration of vision were assumed to be independent of baseline visual acuity but the model submitted by the manufacturer of pegaptanib assumed greater clinical benefits to be associated with better baseline vision. The Committee considered it plausible that people with better pre treatment visual acuity are likely to benefit more from treatment than those with lower pre treatment visual acuity. This could be for example because wet AMD lesions that have caused greater deterioration in visual acuity are also more likely to have caused permanent structural damage which reduces response to anti VEGF treatment.*”
- 15 The Institute accepted the manufacturer's submission that outcomes for anti-VEGFs are dependent on baseline visual acuity and also the plausibility of that view on theoretical grounds.
- 16 The Institute has seen the results of the MARINA and ANCHOR studies. The MARINA trial showed (fig 2c) that there is no improvement in acuity for those with a

starting acuity 6/60 or worse, though there was a very small improvement in ANCHOR (fig 1d). The major and considerable improvements in acuity are obtained in those patients early in the disease with acuity 6/12 or better (MARINA fig2b; ANCHOR fig 1c).

17 The PCT would therefore suggest that the FAD is perverse given:

17.1 The acceptance in paragraph 4.3.7 that outcomes are dependent on visual acuity

17.2 The use of sub group analysis in other Technology Appraisals, and within this FAD in relation to pegaptanib

17.3 The clear evidence from ANCHOR and MARINA

17.4 The health stated utilities used in the economic model

18 In the Institute's Guide to the Methods of Technology Appraisals Paragraph 3.4.4.1 states:

*The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence on equity may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in population groups, **evidence on differential treatment effects in population groups**, and epidemiological evidence on risks or incidence of the condition in population groups.*

And section 5.9.5 (Presenting analysis of clinical and cost effectiveness for patient subgroups) continues:

5.9.5.1 For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be reflected in the analysis by the provision of separate estimates of clinical and cost effectiveness for each relevant subgroup of patients. The characteristics of patients in the subgroup should be clearly defined and care should be taken to justify the clinical basis for the subgroup differences. The uncertainty around estimates of parameters specific to the subgroup should be fully reflected in the analysis.

5.9.5.2 Given the Institute's focus on maximising health gain from limited resources, it is important to consider how clinical and cost effectiveness may differ because of differing characteristics of patient populations.

The PCT therefore considers that recommending treatment to a visual acuity of 6/96 fails to follow its own guidance and therefore falls under Ground 1, failure to follow procedure.

Ground 3: The Institute exceeded its powers.

19 Paragraph 1.1 (Guidance) concludes by stating :

“and

- *the cost of treatment beyond 14 injections in the treated eye is met by the manufacturer. “*

20 In FAD paragraph 4.3.9 it is acknowledged that :

“for some patients it would be appropriate to continue treatment beyond 2 years into the third or even fourth year. This would result in additional drug, administration and monitoring costs, which were not included in any of the economic models.”

Whilst FAD paragraph 4.3.22 states that the Appraisal Committee:

“ noted that the feasibility and administrative burden on the NHS of such a scheme would need to be considered in appraising the cost effectiveness of ranibizumab within such a scheme. Additionally, continued administration and monitoring costs would also need to be considered as patients would require regular re-assessment on a monthly basis to monitor the progress of their disease. The Committee estimated that ranibizumab was likely to be cost effective if the cost of treatment to the NHS was limited to 14 injections in the treated eye.”

21 Novartis, the manufacturer, has been asked by the PCT whether it will fund “ the cost of treatment beyond 14 injections”. Mr S Meadows, (Healthcare Funding Manager) advised the PCT, by telephone, during week commencing 7 April 2008 that it will fund only the additional drug costs.

22 The Institute has clearly indicated that its recommendations are dependent on funding by Novartis of treatment beyond 14 injections, yet Novartis has declined to agree to that condition. The Institute has no power to mandate any manufacturer and has thus exceeded its powers in issuing its recommendations. The Institute appears to have made an assumption that the manufacturer will fund the cost of treatment beyond 14 injections but this is unsupported by evidence.

23 Further the PCT would wish to highlight that there are no Regulations which permit co funding. Setting aside cost effectiveness arguments if Novartis were to provide the drug this could lead to an example of co funding. The Institute will be aware that

a patient is either a private patient or an NHS patient. The Institute is referred to Guidance produced by the Government in 2003 called: A Code of Conduct for Private Practice: Guidance for NHS Medical Staff. That in turn refers to Management of Private Practice in Health Service Hospitals in England and Wales – the Green Book.

- 24 The PCT would also submit that this point would fall under Grounds 1 and 2. Sections 5.10.3 and 5.10.4 of Guide to the Methods of Technology Appraisal concerns the assessment of resource and cost implications of the Institute's Guidance. As the Institute (and the NHS in general) is not in control of a major cost element (that is, the clinic costs after the 14th injection), because Novartis is declining to agree to fund these costs, resource and cost implications are so uncertain that the Institute is unable to fulfil these two paragraphs, failing on Ground 1. The Institute has failed to take into account the evidence that Novartis will not fund clinic costs (or has not properly understood the Novartis offer) and so this issue also falls under Ground 2.
- 25 The PCT reserves the right to amend this document following initial scrutiny of this document by the Institute.