

Mr M Taylor
Appeals Committee Chair
National Institute for Health and Clinical
Excellence
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20 May 2008

By email and fax: 0207 0619 828

Dear Mr Taylor

Final Appraisal Determination: Ranibizumab and Pegaptinib for Age related Macular Degeneration

I am responding on behalf of [REDACTED] of Derbyshire County Primary Care Trust ("the PCT") to your letter of 6th May 2008 concerning the above appeal. Please note that we have been instructed by the PCT to represent them in this appeal. We would be grateful if all correspondence and documents relating to this appeal could be sent to us at the address at the foot of this letter with the above reference.

The background

1. The PCT accepts that for some groups of patients Ranibizumab is a clinically effective drug and appears to be the best medical technology available to treat AMD. The PCT can therefore appreciate that patients with AMD feel strongly that they should be provided with the treatment as part of the National Health Service. We also acknowledge that patient groups have placed NICE under very considerable pressure to approve the technology. We equally appreciate that the manufacturer, Novartis, having developed a clinically effective drug, wishes to sell the drug to the NHS.
2. However the interests of the PCT are not necessarily coincidental to those of patients with a particular condition. The role of the PCT is to ensure that it provides both clinically-effective and cost-effective treatments across the entire range of medical conditions suffered by patients within the Derbyshire area. As we understand NICE's processes, a sample number of PCT's are invited to respond to the Appraisal Consultation Document ("ACD") produced by NICE and those PCTs have the right to appeal against any part of a Final Appraisal Determination ("FAD") where there are good grounds within the NICE system.
3. This appeal is therefore lodged on behalf of the NHS generally to ensure that PCTs are able to make effective use of the limited resources provided to them across their entire populations. As part of that process we would wish to focus the attention of the appeal committee on procedural issues which the PCT feel consider merit further attention.

Ground 1

4. The first ground concerns consultation at the initial stage. We regret that your response suggests to us that the PCT has not yet been able to have explain the background and significance of this point. When NICE commenced this process it named "High Peak and Dales PCT" as one of your consultees for the consultation which commenced on 1st June

Birmingham Cambridge Leeds London Manchester Norwich

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2007. By that stage, as was well known within the NHS, High Peak and Dales PCT had ceased to exist.

5. Our client, the successor body, assumes that the intention of NICE was that Derbyshire County PCT rather than High Peak and Dales PCT should have been the nominated consultee. However our client has no record of receiving any invitation to consult with NICE about this drug. You have referred in your letter to this being as a result of “disorganisation as a result of the merger”. However we would suggest that the primary fault must rest with NICE who were attempting to consult with a body which no longer existed. It was the failure of NICE to remain up to date with changes in PCTs (which were very well publicised) that meant our client did not have had an opportunity to be involved in the original consultation.
6. Our client is unable to say whether an invitation to consult was or was not received by the PCT. We therefore do not accept that it was necessarily a matter of disorganisation at our client’s end. The material, if it was sent, was sent to the wrong statutory body.
7. You have argued that our client had the opportunity to respond to the consultation on the second round and therefore any procedural unfairness from the first round was remedied. However it appears to us that this may not have been the case because one of the key issues raised by our client in the second round of consultation (which was supportive of NICE analysis in the first round) around the correct cohort of patients who could benefit from the treatment did not appear to be properly considered as part of the second round of consultations. More details are provided about this issue under Ground 2.
8. If, contrary to the impression given by the responses provided by NICE to the second round of consultation, NICE are able to demonstrate to the Appeal Committee that the committee did properly consider the issues raised in Ground 2, we would accept that there is no material benefit in pursuing the procedural errors which led to a lack of consultation under this ground. If however NICE are unable to provide clear and compelling documentary evidence to show that the issues under ground 2 were properly considered either as part of the second stage of consultation or later, then the lack of opportunity to focus the mind of the committee on these issues in a first stage consultation remains important and would appear to us to be a proper ground of appeal.

Ground 2

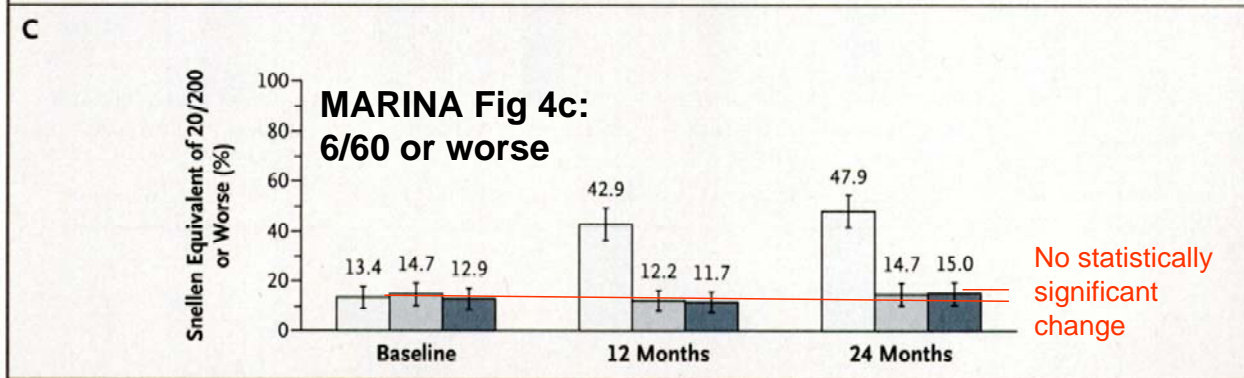
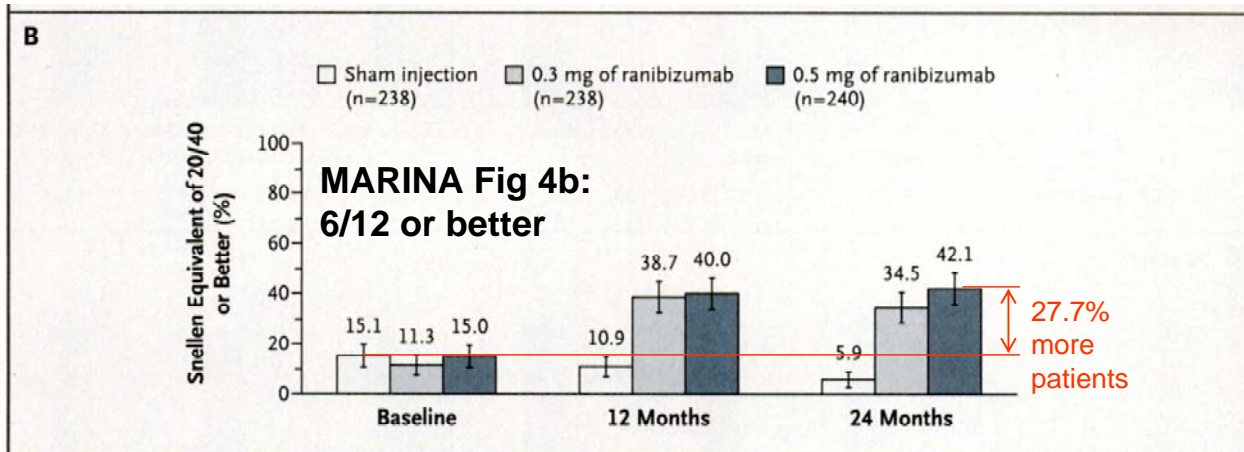
9. We apologise if our original grounds of appeal did not make this matter clear. The issue we wish to focus upon is whether there is proper and sufficient evidence that Ranibizumab is a cost effective treatment for patients whose initial visual acuity is between 6/60 and 6/96. We will refer to this group of patients as a “sub-group” of the main cohort who are patients defined within the FAD. It may be helpful if we set out the basis of our concerns in a little more detail.
10. NICE recognises that medical technologies can have differential effects on different cohorts of patients who suffer from the same medical condition depending on the characteristics of the medical condition suffered by the patients. Even within a defined patient condition cohort, the effects on individual patients of the application of a medical technology can differ markedly with some patients having great benefit and others having very limited if any benefit. The issue for any commissioner of healthcare services is “what is the likely benefit for this patient of this proposed treatment?”. The NICE

Guide to the Methods of Technology Appraisals rightly reflects this by considering the average effect of the technology for patients generally within the cohort¹.

11. However even if the average response to a technology across the cohort produces an ICER which is acceptable to the NHS, if the patient cohort in the recommendation is defined too widely it is likely that treatment will be provided to a sub-group of patients where the average health gains amongst those patients are not sufficient to justify the expense. That would not be a justifiable use of limited NHS resources. Conversely, if those patients are excluded then, by definition, the average response for the balance of patients left in the cohort will be improved and the ICER will fall thus producing more cost effective treatment.
12. In approaching this matter in relation to Ranibizumab there are, in our submission, two critical factors:
 - a. The degree of either sight improvement and/or reduction in the rate of sight deterioration suffered by patients in this sub-group (namely the group of patients whose initial visual acuity is worse than 6/60 compared to the control group); and
 - b. The degree of health utility loss for patients in this sub-group.
13. The December 2007 ACD recognised this and stated at Paragraph 4.2.3.12 as follows:

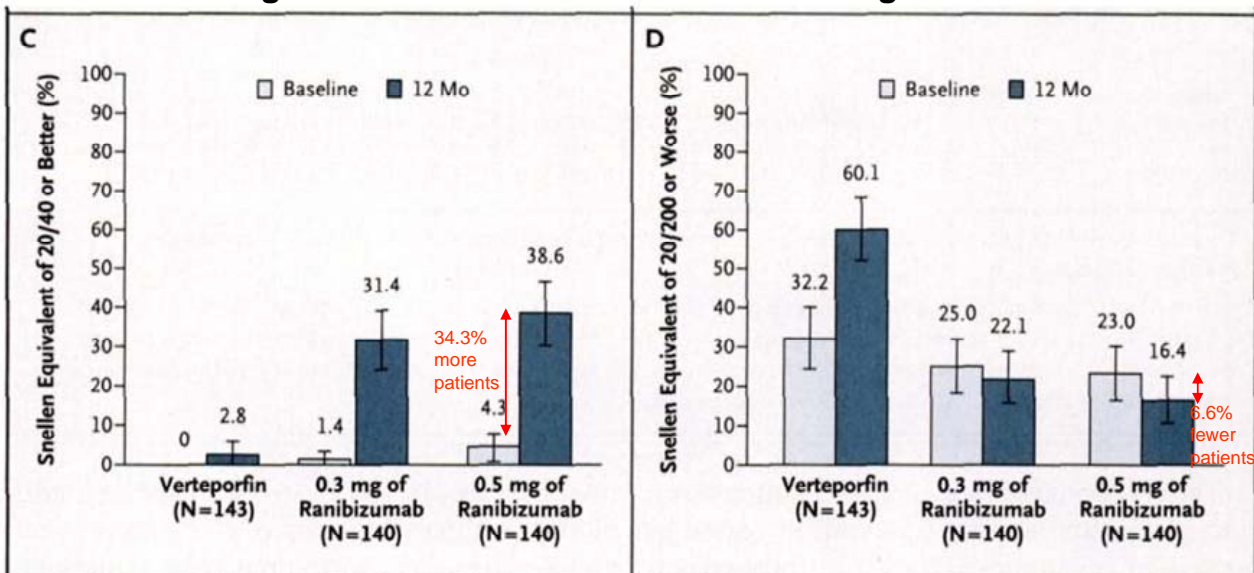
“In sensitivity analyses, varying the distribution of initial visual acuity has a significant effect on the ICER. A cohort equally split between the 6/12-6/24 and 6/24-6/60 states produced an ICER of about £35,900, while a cohort with initial visual acuity of 6/24-6/60 produced an ICER of about £46,300”
14. This is consistent with the evidence from the Anchor and Marina trials which show that the improvements in eyesight shown by those patients with a greater initial visual acuity are not replicated by those who start with a visual acuity of less than 6/60. The best that can be said for this group is that, for a proportion, their eyesight does not deteriorate as much as it would if they were not provided with the drug, but it is unlikely to improve to any marked extent. Thus the clinical findings for this group are to be contrasted with the effects on those patients who start with better eyesight.

¹ See para 3.2.1.1 of the Guide to the Methods of Technology Appraisal



ANCHOR Fig 1c: 6/12 or better

ANCHOR Fig 1c: 6/60 or worse



Sight is improved in 26.6% & 34.3% of patients with good starting VA but by in only 6.6% or not at all in those with very poor VA.

15. In considering the first of the factors set out in paragraph 12(a) above, the committee appear to have recognised that this was important as shown at paragraph 4.3.7 of the FAD which states:

“The Committee considered whether the clinical effectiveness of the anti-VEGFs varies between subgroups defined according to baseline visual acuity”

16. However the second factor, loss of health utility compared to the control group, is equally important. The loss of health utility from a reduction of eyesight of 6/60 to 3/60 is just 5%. This is compared to a loss of utility from, for example, 6/12 to 6/60 of 33%. In practical terms we understand that this means that the reduction in quality of life is assessed to be far greater for someone whose eyesight falls from 6/12 to 6/60 than someone whose eyesight falls from 6/60 to 3/60. Against this it must be noted that the costs for treating two such patients with this drug are largely identical. The big gains in quality of life are to be gained from, first improving, and then preventing a decline, in visual acuity to 6/60, but not treating beyond that point when there is no improvement and much less potential loss of quality of life. It must therefore follow that, for this sub-group, the ICER is higher than for the sub-group of patients who start with a better visual acuity. Table 4.19 of the Assessment Report has been amended a little to illustrate the issue more clearly:

Table 4.19 Health state utilities used in economic model					
Visual acuity range	Mean Utility	marginal change	cumulative change from 6/6	Standard deviation	95% CI
6/6	1	0	0		
>6/12	0.89	-0.11	-0.11	0.16	(0.82 – 0.96)
6/12 to 6/24	0.81	-0.08	-0.19	0.2	(0.73 – 0.89)
6/24 to 6/60	0.57	-0.24	<u>-0.43</u>	0.17	(0.47 – 0.67)
6/60 to 3/60	0.52	<u>-0.05</u>	-0.48	0.24	(0.38 – 0.66)
<3/60	0.4	-0.12	-0.6	0.12	(0.29 – 0.50)

17. In the light of this evidence, our client challenges the conclusion of the Committee in paragraph 4.2.3.10 of the FAD where they stated as follows:

“In sensitivity analyses, varying the distribution of initial visual acuity had very little effect on the ICERs for Ranibizumab. For example, for minimally classic lesions compared with best supportive care, a cohort equally split between the 6/12–6/24 and 6/24–6/60 states produced an ICER of £25,179 per QALY gained, whilst a cohort with initial visual acuity of 6/24–6/60 produced an ICER of £25,268 per QALY gained”

18. We have the following complaints about this paragraph to demonstrate that the rigorous standards the NHS is entitled to expect from NICE have not been followed in this case:

- a. It does not explain the reasons for the deviation from Paragraph 4.2.3.12 of the ACD ,set out above, which reached the opposite conclusion;
- b. It only compares ICERs for initial visual acuity patients with eyesight of 6/60 or better but not those with an initial visual acuity of 6/96, but then recommends the

treatment for patients with initial visual acuity patients with eyesight of 6/96 where the evidence suggests there may well be different ICERs;

- c. It uses one sub-group as an example – patients with minimally classic lesions – and seeks to draw a general conclusion from the ICER calculations relating to that sub-group alone. That is an impermissible step to take given that there is evidence to the contrary for patients as a whole; and
 - d. With diminishing clinical effectiveness and diminishing loss of utility, the Committee ought to have carefully considered, with proper economic models, the extent to which ICERs increased depending on the initial visual acuity of patients. However the committee did not have that information because, as the paragraph set out above notes, its economic modelling on cost effectiveness did not take the initial visual acuity of patients into account.
19. Thus the committee ought to have refused to adopt recommendations which were based on flawed economic models for the treatment.
20. Despite these shortcomings the committee, at Paragraph 4.3.25 of the FAD, went on to accept that the entire patient group, which were subject to the manufacturer's trial, should be included within the recommendations. This is illogical because the ICER for the sub-group of patients within that overall cohort who commenced the trial with a visual acuity below 6/60 must be substantially higher than the average figures given and the ICER for those whose initial eyesight is better than 6/60 must be lower.
21. The PCT's case is that no reasonable committee being presented with such evidence could reasonably have come to the view that the cohort should be defined by those patients who happened to be included within the manufacturer's study rather than considering sub-groups within that cohort. Indeed, identifiable sub-groups should only be included within the FAD if there is a convincing case, supported by both clinical evidence and economic studies which justify the inclusion of the sub-group within the FAD.

Disclosure Request

22. The PCT seeks disclosure of:
- a. The minutes of any meetings at which the above issue was discussed including the meetings referred to in the FAD;
 - b. Any technical reports or other material which was used by the committee to reach the conclusions set out in paragraph 4.2.3.10 of the FAD (and Paragraph 4.2.3.12 of the Second ACD) and any sensitivity analysis which was undertaken; and
 - c. Any reports, academic material or any other documentation which is held by NICE which touches upon the above issues.

Ground 3: Request for clarification

23. We are grateful that you have accepted this as a proper ground of appeal. In advance of the appeal, can we invite the committee to clarify the terms of the recommendation. The recommendation is that:

“the cost of treatment beyond 14 injections in the treated eye is met by the manufacturer”

24. As we understand it there are 3 separate elements of cost associated with this technology:
- a. The drug costs;
 - b. The staff time and other costs associated with the administration of the drug²; and
 - c. The monitoring costs between injections.
25. There are potentially three sources to pay for these costs:
- a. The manufacturer;
 - b. The NHS bodies; and
 - c. Individual patients.
26. Does the Committee understand this recommendation to mean:
- a. After 14 cycles the manufacturer is expected to provide the drugs at nil cost to the NHS with the remainder of the monitoring and treatment costs being met by NHS bodies; or
 - b. After 14 cycles the manufacturer is expected to provide the drugs at nil cost to the NHS and to compensate the NHS the monitoring and treatment costs; or
 - c. After 14 cycles the manufacturer is expected to provide the drugs at nil cost and the costs of treatment and monitoring will be met by the patient; or
 - d. None of the above, in which case please explain how this recommendation is supposed to work?

Request for disclosure

27. Paragraph 4.3.22 refers to this being “a suggestion from the manufacturer”. In order to prepare for the appeal can you please disclose to us details of all documents passing between NICE and/or the members of its committees and the manufacturer and all NICE internal documents which make any reference to the background of this proposal.
28. Given the remit of NICE to assess and then issues recommendations around the cost effectiveness of medical technologies, it is our case that no reasonable committee could have published a recommendation along the above lines without being clear about the basis upon which it would be supposed to operate.

Consequences of the NHS bearing continuing costs

29. Out client considers that on the basis of the evidence from all the trials, in particular PIER, that the most likely scenario is that once patients are started on treatment it will need to continue, at least for some patients, for the rest of their lives or until their eyesight deteriorates beyond help. NICE has accepted that treatment will need to

² For example, the committee noted that there was a considerable difference in costs depending on whether they were administered in an outpatients setting or as a day operation.

continue beyond 2 years, but we are concerned that this is the point at which NICE ceased to consider costs in its economic assessments. That is justifiable if all the costs after 2 years are to be borne by the manufacturer but in any other scenario the FAD will result in the NHS having a large element of anticipated costs that are excluded from the economic models.

30. If treatment is to the PrONTO regimen then the PCT estimates that repeat testing and injection clinic costs accruing after year 2 (14 injections) would represent 55% of lifetime treatment costs even if Novartis provide Ranibizumab free of charge. This would therefore more than double the ICER.
31. The PCT therefore consider that, within the current NICE Guidelines, it would be perverse and impermissible to publish the FAD before the exact terms of the post 14 cycle arrangements have been concluded.

Pfizer Appeal

30. We note that an appeal by Pfizer relating to Pegaptinib has been listed for hearing before the Appeal committee at the same time as our appeal. Would you kindly provide us with copies of all relevant documents relating to that appeal.

The importance of this appeal

If this FAD is implemented by a Technology Appraisal Guidance in like form, the result will be a diversion of millions of pounds of NHS resources to fund Ranibizumab (known as Lucentis) away from other treatments. This matter will therefore have very serious implications for the NHS and, for the reasons set out above, we consider that our clients are entitled to challenge the basis for the diversion of such resources from more cost effective areas of healthcare in which our clients would wish to invest.

We consider that there are entirely proper Grounds to support an appeal within your own terms of reference. In particular we consider that Ground 2 could be considered under any of the categories in paragraph 4.6.3 of the Guide to the Technology Appraisal Process. We consider that it is only fair to you at this stage to indicate that, in the event that you are not minded to accept that the above constitutes a proper Ground of Appeal, the PCT will reserve all its rights to challenge such a decision.

We also do not consider that we could properly represent the interests of our client in this appeal without disclosure of the relevant documents and trust that copies will be forthcoming in sufficient time to allow us properly to prepare for this appeal.

As the hearing is fixed for 30th June 2008, may we hear from you by **Monday 2nd June 2008** at the latest with the above items of disclosure and with the requested particulars.

Yours sincerely


for Mills & Reeve LLP

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