Pegaptanib and ranibizumab for treatment of age-related macular degeneration (AMD) – Additional analysis to inform appraisal process

RNIB and Macular Disease Society

Patient group response

October 2007

Introduction

1. In this document the RNIB and Macular Disease Society respond jointly to the additional documentation sent out to stakeholder participating in the appraisal of pegaptanib and ranibizumab.

2. We welcome the fact that NICE has decided to commission further analysis of the available data to establish whether ranibizumab and pegatpanib are cost-effective treatments for wet age-related macular degeneration. We see this decision as a necessary response to the serious weaknesses in the initial proposals set out in the appraisal consultation document (ACD) issued in June 2007. If adopted the criteria proposed in the ACD would have barred 80 per cent of patients from treatment, an unacceptable outcome from the point of view of patients and the organisations that represent them in this appraisal process.

3. A number of comments on the additional documentation provided are set out in this document. However, along with other stakeholders, we are not confident that this additional analysis will result in an evidence-based decision on the cost-effectiveness of either treatment. The complete documentation contains approximately 100 ICERs without any indication as to which of the assumptions used to produce these are most sensible to make. To give just three examples:

3.1. Several ICERs are given for the cost-effectiveness of pegaptanib depending on whether or not it has a disease-modifying effect and depending on the patient's baseline visual acuity at the start of treatment. The report states that the disease-modifying effect is key to showing that treatment for patients with a visual acuity between 6/12 and 6/24 is cost-effective. However, no indication is given as to whether the Appraisal Assessment Group should assume that a disease-modifying effect exists. On what basis will that decision be made?

3.2. Another key element of the models is the percentage of blind and partially sighted people receiving community care support. The report suggests that incremental cost and ICER were

sensitive to alternative assumptions regarding the proportion of blind people receiving community care support. The alternative proportions chosen were six, 17 and 25 per cent. Again, the question is on what basis the Appraisal Group will decide which of these figures to use.

3.3. A third example is the use of different utility values. The new documents introduce utility values presented by Espallargues and colleagues. ICERs calculated with Espallargues values are two to three times higher than the base case utility values. Even though they come with a health warning they are included in the models, in theory presenting the Assessment Group with an option to refuse approval of both pegaptanib and ranibizumab for use on the NHS.

4. There are additional issues around the assumptions about the frequency and cost of treatment. Importantly, a study on the link between AMD and depression is introduced that concludes that there is no link between early and late AMD and depression. As the summary states “the weaknesses of the population studied may justify the exclusion of this study”. We would strongly urge the Appraisal Committee to disregard the study findings since there is no doubt about the strong link between wet AMD and depression and this is what the Committee should focus on. In our detailed comments below we provide a statement from an eminent expert in the field of sight loss and depression to support our assessment of this study.
5. In summary, we feel that the additional analysis provided does nothing to allow a clearer conclusion as to the assumptions that should be used for the cost-effectiveness estimates for pegaptanib and ranibizumab. On the contrary, the data provided is highly confusing and presented in a way that is only fully accessible to health economists.
3. From our experience as patient experts at the April meeting of the Appraisal Committee we are assuming that the new data will be presented to the Committee by one of its members. It is that presentation that will guide the Committee in its deliberations and it is that presentation that we should be given to enable us to provide meaningful comments. Just sending out these documents

makes the additional consultation that NICE promised meaningless and questions the validity of the whole consultation process. This is why we have joined the Royal College of Ophthalmologists in calling for a second ACD.

4. Finally, we would like to remind the members of the Appraisal Committee of a recent statement by Lord Darzi in his report on the future of the NHS published in October 2007[1]: "the NHS needs to move away from cost containment and seek to harness innovation".
5. In light of the imperative to harness innovation rather than focus on cost containment, we would like to urge the Appraisal Committee to focus at least for a few moments on the fact that its decisions have far-reaching implications for real people, and in this case, older people who have paid into the NHS all their lives. If a patient-centred approach is to be more than pure rhetoric we need to garner the benefits of new treatments to help older people retain their quality of life or even regain it as a result of treatment. This is what it means to harness innovation.
6. Below please find a striking case study to illustrate the difference a positive decision to approve the new anti-VEGF treatments on the NHS will make.

[1] Department of Health: Our NHS, our future: NHS next stage review – interim report. Published date: 4 October 2007

[redacted], West Yorkshire

80 year old Mrs [redacted] developed wet AMD in her left eye after having lost some sight in her right eye due to dry AMD. She contacted our advocacy service at the beginning of August 2007 because she felt unable to pay for private treatment. At this stage her sight in her left eye had deteriorated considerably. She describes a big black blob in her left eye. She was still able to go out on her own even though she had problems with steps. However, she could no longer read anything but the large headings in newspapers and was unable to pursue her lifelong hobbies of knitting, embroidery and sewing. "Not being able to do my hobbies was a big blow. More than that though, I started to see my life drift away to darkness. I was no longer able to see the things I wanted to see such as the birds outside. The most difficult part was the fear of waking up one morning to find that my sight had gone completely. The hours I spent lying awake at night, unable to sleep… it was really dreadful!" Mrs [redacted] said that having wet AMD not only affected herself. Her husband was very worried about her and what might happen if she ended up on her own one day without anybody to look after her.

Eventually, her PCT decided to fund her treatment and she has now had two injections with Lucentis. "It is difficult to describe the difference. After just two injections I have had some improvements to my sight. The light is coming back and also the colour. And I no longer spend sleepless nights worrying about what may happen. It has made a huge difference to my quality of life and I definitely feel that everybody with wet AMD who can benefit should have the new treatments."

Additional comments

Second eye policy

7. We continue to uphold our arguments regarding the importance of treating patients who present with their first eye. We believe that the data presented in the additional analysis is not helpful because it states the obvious: it is more expensive to treat two eyes than to treat one eye. However, it makes no attempt to assess the quality of life improvements for patients whose sight in the first eye is saved and does not present any ICERs. In the light of medical opinion supported by the Royal College of Ophthalmologists we continue to argue that second eye policy would be simply unacceptable.

Use of pegaptanib

8. The new analysis appears to support the argument that pegaptanib should be made available to patients with a visual acuity of 6/12-6/24. While we recognise the cost-effectiveness arguments for this our position remains that pegaptanib should be made available for use in all patients irrespective of baseline visual acuity as long as the treating clinician believes that this is the best course of action for an individual patient. In reality, most patients will be given ranibizumab. A decision to give pegaptanib on medical grounds should remain possible where patients are unlikely to tolerate ranibizumab.

Rationing of treatment to exclude all lesions except the 20 per cent of patients with predominantly classic CNV

9. **Cost effectiveness**

9.1. Most of the ICERs relating to the use of ranibizumab seem to lie below the £30,000 threshold that NICE appears to apply to its appraisals, many of them are even below the £20,000 threshold depending on the assumptions made. This appears to apply to all lesion types. Worryingly, there are no indications as

to which scenarios the Assessment Committee should adopt. Treatment costs based on different injection frequencies and different treatment costs continue to vary widely as do the results when different utility values are used.

9.2. While we welcome the efforts to include some of the costs of blindness that we highlighted in our response to the ACD, we continue to question some of the cost assumptions and the categories used. Most importantly, we would have hoped that the additional analysis would have enabled the Southampton Health Technology Assessments Centre to produce one figure for the overall cost of blindness that could then be varied according to up-take. The figures provided show a rather one-dimensional view of the costs of sight loss which focuses entirely on the up-take of community care service. If we accept that this is the deciding factor we are still faced with the question as to what uptake level reflects reality. Our own data suggests that the uptake is definitely higher than 6 per cent but we are not sure that there is enough evidence available to decide whether it should be 17 per cent or indeed 25 per cent. We would recommend the use of the 25 per cent figure which may be on the high side but would compensate for the fact that NICE is not allowed to take account of the vast costs of blindness to society caused by the need for informal care, loss of productivity and the provision of benefits and allowances.

10. AMD and depression

10.1. The article by Sun et al. contained in the additional documentation is rightly seen to have major weaknesses that should lead to its exclusion. Concerns do not only relate to the population studied and the number of people participating out of the potentially eligible participants in the Cardiovascular Health Study. According to Amy Horowitz, Professor of Geriatrics and Adult Development at Mt Sinai School of Medicine, and expert on AMD and depression, “the most problematic limitation of the study is that there is no evidence that subjects defined as having early AMD had any functional limitations because no acuity or other vision measure was taken. In the absence of functional problems there is no reason to expect a relationship

with depression since there is extensive evidence to support that it is not the diagnosis of a disease that is associated with depression, but the resulting limitations on daily life. It is precisely because persons with more advanced AMD are likely to have extensive functional limitations, especially in very valued activities such as reading and driving, that a strong relationship between AMD and depression has been documented in numerous studies." And since no AMD data is available from the beginning of the study to provide a baseline it is possible that many of the participants who were diagnosed with early AMD were not even aware that they had the condition. Many consultants only talk to their patients about AMD when it is clear that it is starting to impact on the patients' ability to function normally in everyday life. Dr. Horowitz continued: "Also, since only 29 participants were diagnosed with late AMD, the study probably did not have sufficient power to find a relationship between late AMD and depression."[2] In light of these comments we urge members of the Assessment Committee to disregard the findings of this study and go back to our previous submissions which contain data on the increased risk of depression in patients with wet AMD (who by definition have late stage AMD). This is the data that proves that failure to treat patients with wet AMD will result in unnecessary depression and associated health resource use. And this is the data that should inform the Committee's discussions.

Final Comments

11. We have done our best to make sense of the additional analysis presented to us and have provided comments accordingly. However, as stated above, we do not believe that the data on its own will make it easier for the Assessment Committee to decide whether their initial recommendation to deny treatment to 80 per cent of patients was justified or not. Without a presentation that pulls together all the evidence and provides assistance with its interpretation it is unlikely that the members of the Committee will be benefit from the additional analysis.

[2] Comment provided on 19 October 2007 in support of our submission.

12. Since stakeholders will not participate at the meeting we urge NICE to issue another ACD that clearly states how the data was presented to help the Appraisal Committee with its interpretation of the evidence and explains how the Committee reached agreement on any revised recommendations.

13. Stakeholders should then be given an opportunity to comment on this ACD. This additional step is essential to safeguard the transparency and fairness of the process. We believe that it should not result in an extension of the deadline for issuing guidance (currently March 2008). At present NICE is predicting four months between the Appraisal Committee meeting and the Final Appraisal Document. We believe that this gap could be shortened to accommodate the additional consultation that we see as absolutely vital.

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The Macular Disease Society

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RNIB