

<b>HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal on Ranibizumab and Pegaptinib for AMD – Assessment Report</b>	
<b>TO: NICE</b>	<b>FROM: NHS Quality Improvement Scotland</b>

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### **General comments**

1. Both pegaptanib and ranibizumab represent a **major advance** in the management of AMD and offer treatment for previously untreatable subgroups of AMD with a low incidence of side effects (particularly if guidance on intravitreal injections is strictly adhered to). Such treatments will significantly improve the outlook for many patients.
2. As a clinician working with patients with AMD I found this a most comprehensive and exhaustive evaluation using the most rigorous methodology possible. I found the cost effectiveness analysis quite confusing and complex with numerous assumptions which are questionable. For someone who is not an expert in health economics to comment on such detailed analysis is difficult and a summary or conclusion in plain language would be appreciated. The authors indicate the difficulties arising from the assumptions made in modelling the cost effectivity analysis. As I am not qualified to comment in depth on the health economic aspects of the appraisal, my comments reflect my experience as a clinician. There is a lack of any firm recommendations or conclusions and I presume and hope these will be made in later drafts.
3. Many sections in the report relevant to the clinical effectiveness are blanked out and one cannot comment on these fully.

4. I find it surprising that the evaluation does not make any specific **recommendations** or conclusions regarding the merits of either drug. This would be helpful and I presume they will be made in later drafts. Although there are difficulties in comparing pegaptanib and ranibizumab due to the differences in study populations and comparators the clinical effectiveness of ranibizumab appears greater. The probability of being cost effective depends on the willingness to pay threshold. At a willingness to pay threshold of £20,000 and £30,000 per QALY ranibizumab is the more cost effective drug. Although a head to head trial of ranibizumab and pegaptanib would answer which is more effective can we not conclude that on the basis of current knowledge and analysis that ranibizumab is the more cost effective and recommend it?

### **Specific comments**

1. There are of necessity a large number of informed assumptions regarding the **numbers of patients requiring treatment**. The epidemiological data regarding the different subtypes of AMD is inconsistent and calculations of the numbers of patients requiring treatment may not reflect actual numbers presenting in the UK. The VPDT cohort study currently being undertaken in the UK may offer realistic statistics on actual numbers presenting with different subtypes of wet AMD.
2. The **true cost of visual impairment** is difficult to determine accurately. It should be noted that many patients decline to be certified blind or partially sighted and the true figure may be greater than that estimated.
3. **The response of different subtypes of wet AMD** is of great interest and may indicate different outcomes to treatment with both pegaptanib and ranibizumab. There may be subtypes which respond well and others which respond poorly. The identification of subgroups which are non-responders and subgroups which respond significantly better is extremely relevant. The VISION study analysed different subgroups but found inconsistent results between the US and the European cohorts. The best results with pegaptanib were seen in the minimally classic and occult CNV patients. We now recognise different forms of occult

AMD e.g. retinal angiomatous proliferation, serous retinal pigment epithelial detachments (PEDs), fibrovascular PEDs etc. None of the studies analyse these different groups and it is likely that the outcomes to treatment differ in each type. This would be a relevant area of research. The ANCHOR and MARINA trials found ranibizumab to be effective in all lesion subtypes but subgroups of occult are not analysed.

4. **The non-drug costs** are difficult to determine accurately. The need for supplementary investigations such as fluorescein angiography and OCT at many of the visits is debatable. It is likely that with the advent of widespread OCT many less fluorescein angiograms are required – certainly much less than with PDT. The recommended criterion for retreatment with ranibizumab after 3 months is a drop in visual acuity – not any criteria depending on fluorescein angiography. VA and OCT findings are most likely to be the factors determining retreatment.
5. The **drug regime** which was followed in the ANCHOR and MARINA studies and which indicates the best outcomes with ranibizumab is not that accepted by the Committee for Medicinal Products for Human use and recommended by the company in the Ranibizumab licence. There are no RCTs with large numbers of patients using 3 injections over the first 3 months followed by further injections only if the vision drops by 5 letters on the EDTRS chart. (or with 8 injections in the first year and 6 in the second – as used in the cost effectivity calculations). In this respect although this seems a practical approach and improves the cost effectivity significantly compared to 24 injections over 2 years, it is not based on high quality evidence. It is of concern that the effectivity of ranibizumab was reduced in the PIER study where the frequency of treatment was reduced.
6. The end point of treatment remains unclear. Will patients require continued maintenance injections in the long term i.e. past 2 years? This is of great concern. The authors indicate that the validity of extrapolating the 2 year results to 10 years is questionable. The basic pathology which gave rise to CNV has not been removed and recurrent CNV on cessation of treatment is highly likely!

7. What are the recommended criteria for treatment in terms of level of visual acuity? Are we to treat patients with visual acuities less than 6/60 or CF for example? As indicated it is likely that the poorer the initial acuity the less likely the patients are to respond to treatment. Are we to treat occult lesions with VA of 6/9? Guidance is required.
8. Which patients should not be treated? It is obvious that fibrotic inactive late disciform scars should not be treated – what about patients with longstanding partially fibrotic exudative lesions? Should we only treat occult CNV with recent progression of visual loss? The natural history of occult CNV lesions is extremely variable and some lesions may remain static for long periods and some resolve spontaneously. Guidance is required.
9. The implications for service provision are indeed concerning with a huge increase in workload. In many respects the assessment is not as elaborate as that required for PDT and the service provision, particularly in terms of the delivery of repeated intravitreal injections, need not be in specialised units and could be delivered by all eye departments. The workload implications will have major impact on all staff involved in the multidisciplinary team and will require increased staffing including ophthalmologists, optometrists, ophthalmic nurses, ophthalmic photographers and administrative staff. All eye departments will have issues with space and the capacity of treatment facilities with the need to establish ‘clean’ rooms etc.
10. **Nonresponders** - If a patient does not respond to treatment within say 3 injections should treatment be continued? – probably not!
11. The FOCUS trial indicates that PDT combination with ranibizumab has similar results to ranibizumab alone. Can we not make a recommendation stating that ranibizumab should be used alone and not in combination with PDT until further trials prove otherwise?
12. **Research Priorities** As indicated above there are many unanswered questions. The most important however for the NHS is the need to assess the clinical effectivity of Bevacizumab. I consider that better subgroup analysis of the

response of the different types of occult CNV is important in identifying which subgroups respond best and which are non-responders.

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