NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

Ranibizumab and pegaptanib for age-related macular degeneration

The Department of Health and the Welsh Assembly Government have asked the National Institute for Health and Clinical Excellence (NICE or the Institute) to conduct an appraisal of ranibizumab and pegaptanib and provide guidance on their use to the NHS in England and Wales. The Appraisal Committee has had its first meeting to consider both the evidence submitted and the views put forward by non-manufacturer consultees and commentators, and the clinical specialist and patient expert representatives nominated for this appraisal by non-manufacturer consultees and commentators. The Committee has developed preliminary recommendations on the use of ranibizumab and pegaptanib.

This document has been prepared for consultation with the formal consultees. It summarises the evidence and views that have been considered and sets out the preliminary recommendations developed by the Committee. The Institute is now inviting comments from the formal consultees in the appraisal process (the consultees for this appraisal are listed on the NICE website, www.nice.org.uk).

Note that this document does not constitute the Institute's formal guidance on these technologies. The recommendations made in section 1 are preliminary and may change after consultation.

The process the Institute will follow after the consultation period is summarised below. For further details, see the 'Guide to the technology appraisal process' (this document is available on the Institute's website, www.nice.org.uk).

- The Appraisal Committee will meet again to consider the original evidence and this Appraisal Consultation Document in the light of the views of the formal consultees.
- At that meeting, the Committee will also consider comments made on the document by people who are not formal consultees in the appraisal process.
- After considering feedback from the consultation process, the Committee will prepare the Final Appraisal Determination (FAD) and submit it to the Institute.
- Subject to any appeal by consultees, the FAD may be used as the basis for the Institute's guidance on the use of the appraised technology in the NHS in England and Wales.

The key dates for this appraisal are:

Closing date for comments: 14 January 2008

Second Appraisal Committee meeting: 13 February 2008

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

Note that this document does not constitute the Institute's formal guidance on these technologies. The recommendations made in section 1 are preliminary and may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Ranibizumab, within its marketing authorisation, is recommended for the treatment of wet age-related macular degeneration if all of the circumstances apply in the eye to be treated:

- the best-corrected visual acuity is better than 6/60
- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

and

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

1.2 Pegaptanib is not recommended for the treatment of wet age-related macular degeneration.

1.3 People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

2.1 Age-related macular degeneration (AMD) is an eye condition that leads to a progressive loss of central vision. People retain some

peripheral vision, but the ability to see well enough to recognise faces, drive and read is affected, and vision can deteriorate rapidly.

2.2 AMD occurs in two forms, wet and dry AMD. Wet (neovascular) AMD is characterised by the development of immature blood vessels that grow between the retinal pigment epithelial cells and the photoreceptor cells in the centre of the retina, a process known as choroidal neovascularisation (CNV). These vessels easily haemorrhage and cause lesions on the macula, leading to visual impairment. The fovea is part of the macula, and CNV that develops below the foveal area is termed subfoveal CNV. Dry AMD (non-neovascular) is a form of extensive atrophy (wasting) of cells which progresses slowly, whereas the wet form can lead to a rapid worsening of vision. CNV can be subdivided into classic and occult forms according to its appearance on investigation by fluorescein angiography. The classic form is associated with more rapid progression than the occult form. A mixture of classic and occult CNV can occur in the same lesion.

2.3 There are about 26,000 new cases of wet AMD in the UK each year and the condition affects more women than men. The condition usually affects people who are over 50 years old and the risk increases significantly with age. CNV is classified as classic no occult when the CNV lesions are classic with no occult component; predominantly classic when classic CNV forms at least 50% of the lesion but some occult CNV is present; minimally classic when classic CNV makes up less than 50% of the lesion; and occult only when there is no classic CNV present. The most commonly cited risk factor for AMD is cigarette smoking: the risk of developing AMD is 3.6 times greater for current and former smokers than for people who have never smoked.

2.4 Patient management consists of social support, visual rehabilitation and the provision of aids to help with low vision. However, in the 20% of patients with classic no occult subfoveal CNV and a best-corrected visual acuity of 6/60 or better, photodynamic therapy (PDT) is an option. Visual acuity of 6/60 means that the patient can see at 6 metres what someone with normal vision can see from 60 metres away.

2.5 PDT involves injecting verteporfin, a photosensitive drug that remains in the new blood vessels in the eye. This is followed by treatment with a low-powered laser, which activates the drug causing cell death. The aim is to destroy the CNV lesions without damaging the retina, thereby halting or reducing progressive loss of vision. PDT does not prevent new vessels forming; it only treats established pathological vessels.

3 The technologies

Ranibizumab

3.1 Ranibizumab (Lucentis, Novartis Pharmaceuticals Ltd) is a humanised therapeutic antibody fragment that binds to VEGF-A isoforms, thereby preventing binding of VEGF-A to receptors VEGFR-1 and VEGFR-2. VEGF (vascular endothelial growth factor) is a secreted protein that induces angiogenesis, vascular permeability and inflammation, all of which are thought to contribute to the progression of wet AMD.

3.2 Ranibizumab has a UK marketing authorisation for the treatment of neovascular (wet) AMD. It is administered through intravitreal injection at a recommended dose of 0.5 mg. Treatment is started with a loading phase of one injection per month for 3 consecutive months, followed by a maintenance phase in which patients are monitored monthly for visual acuity. If the patient experiences a loss of greater than five letters in visual acuity (on the Early

Treatment Diabetic Retinopathy Study [ETDRS] chart or one Snellen line equivalent), ranibizumab should be administered. The interval between two doses should not be shorter than 1 month.

3.3 Adverse events of treatment with ranibizumab include endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Increases in intraocular pressure have been seen within 1 hour of injection of ranibizumab. The safety and efficacy of ranibizumab therapy administered to both eyes concurrently have not been studied. For full details of side effects and contraindications, see the summary of product characteristics (SPC).

3.4 The cost of a ranibizumab injection is £761.20 (excluding VAT; 'BNF' 54th edition) . The 2-year cost of ranibizumab is about £10,700 assuming 8 injections in the first year and 6 injections in the second year, and about £18,300 assuming 12 injections in the first year and another 12 in the second year as per clinical trial regimen. Costs may vary in different settings because of negotiated procurement discounts.

Pegaptanib

3.5 Pegaptanib (Macugen, Pfizer Ltd) is a pegylated modified oligonucleotide that binds to VEGF-165, inhibiting its activity.

3.6 Pegaptanib has a UK marketing authorisation for the treatment of neovascular (wet) AMD. It is administered at 0.3 mg once every six weeks (9 injections per year) by intravitreal injection into the affected eye.

3.7 Adverse events of treatment with pegaptinib include transient increases in intraocular pressure and immediate (on the day of injection) and delayed intravitreous haemorrhages. Intravitreal injection procedures are associated with a risk of endophthalmitis:

in clinical trials of pegaptanib, the incidence of endophthalmitis was 0.1% per injection. Cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been observed up to several hours after the pegaptanib intravitreal administration procedure. For full details of side effects and contraindications, see the SPC.

3.8 The cost of pegaptanib is £514.00 per injection (excluding VAT; 'BNF' 52nd edition). The 2-year cost of pegaptanib is about £9,300 (9 injections in the first year and another 9 in the second year). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group's systematic review identified two published randomised controlled trials (RCTs) of ranibizumab and two published RCTs of pegaptanib. In addition, two reports of RCTs of ranibizumab were submitted that were unpublished at the time the Assessment Report was written. Outcomes measured in the RCTs included: changes in visual acuity (loss, maintenance, gain, mean change and deterioration to legal blindness), anatomical changes in CNV lesions, visual function questionnaire scores, and adverse events. The main primary outcome measured in the RCTs was loss of less than 15 letters of visual acuity.

Ranibizumab

4.1.2 Four RCTs of ranibizumab (MARINA [minimally classic lesions], ANCHOR [predominantly classic lesions], PIER [all lesions] and FOCUS [predominantly and minimally classic lesions]) were

included in the Assessment Report and the manufacturer's submission. The length of follow-up in the trials varied from 12 to 24 months and the doses used were 0.3 mg and 0.5 mg. The populations in the trials met inclusion criteria including best-corrected visual acuity between 6/12 and 6/96; no permanent structural damage to the central fovea; lesion size less than or equal to 12 disc areas in greatest linear dimension; and evidence of recent presumed disease progression (blood vessel growth as indicated by fluorescein angiography, or recent visual acuity changes). Outcomes were assessed at different time points, and the number and frequency of injections varied among the trials.

4.1.3 Statistically significantly more patients receiving 0.5 mg ranibizumab compared with both sham injection (MARINA study) and PDT (ANCHOR study) lost fewer than 15 letters of visual acuity from baseline to 12 months. A third of the 0.5 mg ranibizumab group gained at least 15 letters compared with 4% of the sham injection group at 24 months in the MARINA study. In the ANCHOR trial, 40% of the 0.5 mg ranibizumab group gained at least 15 letters compared with 6% of the PDT plus sham injection group ($p < 0.0001$). In the FOCUS study, 24% of the 0.5 mg ranibizumab plus PDT group gained at least 15 letters compared with 5% of the sham injection plus PDT group ($p = 0.0033$). In the PIER study, 90.2% of the 0.5 mg ranibizumab group lost fewer than 15 letters compared with about 49.2% in the sham group ($p < 0.0001$)

4.1.4 The MARINA, ANCHOR and FOCUS trials all reported mean increases in visual acuity in the 0.5 mg ranibizumab group compared with baseline. Gains in letters ranged from 4.9 in the FOCUS trial (0.5 mg ranibizumab plus PDT group) to 11.3 letters in the ANCHOR study (0.5 mg ranibizumab group). In the MARINA trial, gains in letters ranged from 7.2 to 6.6 at 12 and 24 months respectively. Corresponding losses in the sham groups were 8.2 letters in the FOCUS trial, 9.5 in the ANCHOR trial (sham

injection plus PDT groups), and 10.4 and 14.9 letters at 12 and 24 months in the MARINA trial; and these differences were statistically significant.

4.1.5 Most adverse events were mild to moderate. Conjunctival haemorrhage was the most widely reported eye-related adverse event, but its incidence varied among the ranibizumab RCTs and it was also common in the control groups. More patients in the ranibizumab group experienced increased intraocular pressure and vitreous floaters than those in the sham injection group. Endophthalmitis affected about 1% and 0.7% of patients in the MARINA and ANCHOR RCTs respectively. The SPC stated that the overall incidence of arterial thromboembolic events from the MARINA, ANCHOR and PIER trials was higher for patients treated with ranibizumab 0.5 mg (2.5%) compared with the control arm (1.1%).

Pegaptanib

4.1.6 The combined results of two concurrent RCTs (one carried out in the USA and Canada, the other at centres worldwide) comparing doses of 0.3 mg, 1.0 mg and 3.0 mg pegaptanib with sham injection were published as the VISION study. A total of 1208 patients with all types of CNV lesion were included. Patients were followed for up to 54 weeks, then for a further 48 weeks after re-randomisation.

4.1.7 In the VISION study, statistically significantly more patients receiving 0.3 mg pegaptanib compared with sham injection lost fewer than 15 letters of visual acuity from baseline to 54 weeks. More patients in the 0.3 mg group gained at least five letters (22%) compared with 12% in the sham injection group ($p = 0.004$). Gains of at least 10 letters were reported for 11% of the 0.3 mg

pegaptanib group compared with 6% of the sham injection group ($p = 0.02$). Few patients (4%) gained more than 15 letters.

4.1.8 Mean loss of letters of visual acuity at week 54 was significantly higher in the sham injection group than in the 0.3 mg pegaptanib group. A mean loss of 7.5 letters was observed in the 0.3 mg pegaptanib group, compared with a mean loss of 14.5 letters in the sham injection group.

4.1.9 The VISION study reported that the risk of non-response at the end of 2 years was lower for patients who stopped pegaptanib after 1 year compared with those who had never received the drug. The Assessment Group considered this to be biologically plausible because anti-VEGF drugs target the underlying disease in AMD. However, it also noted that the decline in the proportion of responders (those losing fewer than 15 letters) from 54 weeks to 102 weeks in the VISION study was the same for patients who received the 0.3 mg dose as for those who had never received the drug (14%).

4.1.10 In the VISION study most adverse events reported were mild to moderate. After 1 year of treatment they were similar among treatment arms except for vitreous floaters, vitreous opacities, and anterior-chamber inflammation. Eye-related adverse events were more common in the study eye among patients in the sham injection group than the 0.3 mg pegaptanib group, suggesting that the preparation procedure itself (which included an ocular antisepsis procedure and an injection of subconjunctival anaesthetic) may be associated with adverse events. Endophthalmitis affected about 1.3% of all patients in the first year. In two thirds of these cases, there had been a protocol violation (for example, failure to use aseptic technique).

4.2 Cost effectiveness

4.2.1 Published economic evaluations

4.2.1.1 The Assessment Group identified 421 publications relating to cost effectiveness in AMD. None of these were fully published economic evaluations of either ranibizumab or pegaptanib. No additional publications were identified from the manufacturers' submissions. Three conference abstracts identified and reviewed model-based evaluations of pegaptanib.

4.2.2 Manufacturers' submissions

4.2.2.1 Both manufacturers provided economic evaluations. The manufacturers' models took an NHS and personal social services perspective. In addition both models used evidence-based data for the first 2 years, after which there was extrapolation based on the life expectancy of the cohort. Both models used a Markov approach with the states being different levels of visual acuity and death. Costs and benefits in both cases were discounted at 3.5%. There was no direct or indirect comparison of the two technologies.

Ranibizumab

4.2.2.2 The manufacturer's submission compared the use of ranibizumab with best supportive care for patients with minimally classic or occult no classic lesions, and with both PDT with verteporfin and best supportive care for patients with predominantly classic lesions. The different types of wet AMD were analysed separately based on results from four RCTs (ANCHOR, MARINA, PIER and TAP).

4.2.2.3 Because the ANCHOR trial did not include a sham injection arm, comparison between treatment with ranibizumab and best supportive care for patients with predominantly classic lesions was made through indirect comparison using data from the TAP study in which PDT was compared with best supportive care. The MARINA

trial data were also used to estimate the natural history of the disease for extrapolating trial outcomes over 10 years.

4.2.2.4 The manufacturer's model for ranibizumab was a Markov model, which was developed to simulate the change in visual acuity levels for cohorts of patients with subfoveal CNV. The model has five health states with visual acuity states ranging from 6/15 (least severe) to 3/60 (most severe). The Assessment Group noted that the manufacturer applied a different dosing schedule from that used in the clinical trials. The MARINA and ANCHOR trials involved 24 injections over 2 years and 12 injections over a year respectively, but in the base-case analysis for the model, 8 injections in the first year and 6 injections in the second year were used with the assumption that the same clinical efficacy would be achieved with this lower dosing frequency.

4.2.2.5 The base-case incremental cost-effectiveness ratios (ICERs) over a 10-year time horizon for predominantly classic lesions were about £4500 for ranibizumab versus PDT, and about £14,800 for ranibizumab versus best supportive care. Also for ranibizumab versus best supportive care, it was about £26,400 for occult no classic lesions, about £25,800 for minimally classic lesions and about £12,000 for all lesion types.

4.2.2.6 The manufacturer's submission states that the probability of ranibizumab being cost effective at a willingness to pay threshold of £30,000 per QALY for patients with predominantly classic lesions when compared with PDT is 100%. Equivalent values for the comparison with best supportive care are 96% for predominantly classic lesions, 59% for minimally classic lesions, and 57% for occult no classic lesions for a threshold of £30,000 per QALY.

Pegaptanib

4.2.2.7 The manufacturer's model for pegaptanib was a Markov-state transition model comparing the cost effectiveness of the licensed dose of pegaptanib (0.3 mg), taken every 6 weeks for a maximum of 2 years, with usual care in the NHS. Usual care was identified as the best supportive care (visual rehabilitation and provision of visual aids) for all patients, with the addition of PDT with verteporfin in patients with predominantly classic lesions.

4.2.2.8 The model has 12 states, defined by declining visual acuity from 6/12 to 6/96 and an additional absorbing state, death. However, a visual acuity of 6/12 is regarded clinically as the point at which the disease is likely to lead to major impairment of quality of life – for example, the point at which a person can no longer drive. The base-case analysis is based on all lesion types.

4.2.2.9 Treatment was stopped if visual acuity dropped below 6/96 or by six or more lines from baseline at the end of a year. This is referred to as scenario A. The cost effectiveness of adopting an alternative stopping rule with a higher threshold of visual acuity (6/60) for stopping pegaptanib treatment, labelled scenario B, is also reported in the submission. Cycle length in the model is 6 weeks, and there is a 10-year horizon (life expectancy of patients with a mean age of 77).

4.2.2.10 In the base case, the ICER over a 10-year time horizon was about £15,800 for scenario A and about £14,200 for scenario B. Results of sensitivity analyses carried out by the manufacturer showed that the costs and probabilities of receiving visual impairment services and the model time horizon had a significant effect on the ICERs. For example, the ICER for a 3-year time horizon was between £55,000 and £60,000 per quality-adjusted life year (QALY), reducing to £30,000 per QALY when the time horizon was increased to 5 years.

4.2.3 The Assessment Group model

4.2.3.1 The Assessment Group's model evaluated the cost effectiveness of ranibizumab and pegaptanib compared with current practice (PDT with verteporfin for classic no occult lesions or predominantly classic lesions, and best supportive care for all lesion types). They used the following clinically accepted categories of response: intermediate vision loss (loss of 15–30 letters) and severe vision loss (loss of more than 30 letters). The estimated impact of these changes on visual acuity was measured using a Markov-state transition model.

4.2.3.2 A six-state Markov model was developed and the rate of disease progression was expressed as the probability of progressing to a different level of visual acuity health state in each model cycle. The model extrapolated the effects of the 2-year trial period to 10 years in both arms of the model. Given that ranibizumab and pegaptanib treatments are assumed to have stopped by year 2, benefits were assumed to decline at the same rate as those for usual care, although from a higher level of visual acuity.

4.2.3.3 The costs of adverse events of the treatments were also included in the model. Health state utilities reported by Brown et al were used as the Assessment Group considered them to be the most credible published utility values for visual loss associated with AMD.

Ranibizumab

4.2.3.4 The base-case ICERs over a 10-year time horizon for predominantly classic lesions were about £15,600 versus PDT, and about £11,400 versus best supportive care. For minimally classic lesions and occult no classic lesions they were about £25,100 versus best supportive care.

4.2.3.5 The Assessment Group indicated that as the time horizon is reduced from the extrapolated 10 years the ICERs increase. For

example, in sensitivity analyses where the time horizon was reduced from 10 years to 5 years the ICER increased from a range of £11,000–£15,000 to a range of £16,000–£43,000 depending on lesion type.

4.2.3.6 In sensitivity analyses, reducing the number of injections from 12 to 9 reduces the ICER from about £15,600 to about £6,900 (a reduction of 56%) for predominantly classic lesions in comparison with PDT and from £11,400 to about £6,100 (a reduction of 47%) for the comparison with best supportive care. For patients with minimally classic and occult no classic lesions, with an assumed maximum treatment duration of 2 years (as observed in the MARINA trial), reducing the number of injections in the first year of treatment from 12 to 9 (with a further reduction from 12 to 6 injections in year 2) reduces the ICER considerably from about £25,100 to about £12,600. The Assessment Group assumed that the QALY gain would not differ with changes in the number of injections.

4.2.3.7 In a sensitivity analysis, ICERs increased when the injections were costed as day-case rather than outpatient procedures. In particular for patients with predominantly classic lesions receiving a maximum of 1 year's treatment, incremental costs increased by around 70% for the comparison with PDT and around 60% for the comparison with best supportive care. The ICER increased from about £15,600 to about £26,100 for the comparison with PDT and from about £11,400 to about £17,800 for the comparison with best supportive care. For patients with minimally classic and occult no classic lesions, the ICER increased from about £25,100 to about £35,200.

4.2.3.8 The cost-effectiveness estimates were most sensitive to assumptions over uptake of visual support services (estimated as the proportion of patients with visual acuity of less than 6/60

receiving services).. Using high uptake and high unit cost estimates produces a situation where ranibizumab is dominant (with a lower cost and better outcome) compared with either PDT or best supportive care for patients with predominantly classic lesions. However, when low costs and medium uptake assumptions are used, the ICER generally increased to about £20,000 from baseline.

Pegaptanib

4.2.3.9 The Assessment Group estimated the base-case ICER for pegaptanib (all lesion types) compared with usual care to be £31,000 per QALY over a 10-year time horizon.

4.2.3.10 The Assessment Group carried out sensitivity analyses of different assumptions used in their model. Time horizon has a strong effect on cost-effectiveness estimates. As the time horizon increases, the incremental cost of pegaptanib reduces and the incremental QALY gain increases. In addition, the excess costs of treatment are all incurred in the first 2 years. The Assessment Group reported that the more rapid disease progression in the usual care cohort leads to increased costs associated with services for visual impairment, which offset an increasing proportion of treatment costs for the pegaptanib cohort.

4.2.3.11 The Assessment Group also performed a sensitivity analysis to reflect the disease-modifying effect of pegaptanib. Based on an analysis of non-response (that is, loss of at least 15 letters of visual acuity from baseline) in patients randomised to stop treatment after 1 year and those who were never treated, it has been suggested that pegaptanib treatment is associated with a 30% reduction in non-response. This relative risk reduction was applied to the estimated transition probabilities for losing three to six lines and losing more than six lines of visual acuity in the sensitivity analyses.

Since this effect has only been demonstrated for patients in the year following discontinuation of treatment, it was first applied only in year 3 of the 10-year model, resulting in an ICER of £42,200.

4.2.3.12 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.

4.2.3.13 In sensitivity analyses, when a higher cost is assumed for providing injections as a day-case procedure, the ICER increases substantially to £47,800. The costs of blindness, in particular the uptake of services (estimated as the proportion of patients with visual acuity of less than 6/60 receiving services), had an effect on cost effectiveness.

4.2.3.14 In a probabilistic sensitivity analysis, pegaptanib had a probability of being cost effective (compared with usual care) of 17% at a willingness to pay threshold of £20,000 per QALY and 58% at a threshold of £30,000 per QALY.

4.2.4 Further analysis by the Assessment Group and the Decision Support Unit

4.2.4.1 After considering the key responses from consultation, the Committee requested additional analysis from the Assessment Group and the Decision Support Unit. The Assessment Group explored alternative assumptions for the main drivers of the economic model: namely the costs of blindness, the costs of administering the injections, the number of injections for ranibizumab, and the utilities used in the analysis. The Decision Support Unit provided similar analyses in the manufacturer's model for pegaptanib; this was requested because the manufacturer's model enabled consideration of differential treatment effects by

subgroup of baseline visual acuity, based on patient-level data to which the Assessment Group did not have access.

4.2.4.2 The Assessment Group compared the cost difference of treating two eyes versus one eye. It found that the additional cost of treating two eyes for pegaptanib ranged from about £9,100 to about £15,700. The analysis took into account mortality, an annual incidence of AMD in the second eye of 10%, a range of injections of between 15 and 17 over 2 years and the variation in the intensity of monitoring disease progression in the second eye. The equivalent cost difference for ranibizumab ranged from £9,900 to about £28,600 using 9 to 24 injections over 2 years. The cost difference varied depending on whether the cost of administering the injection was assumed to be outpatient, using the outpatient costs estimated by the Royal College of Ophthalmologists or day-case costs. The Assessment Group also noted that when the intensity of monitoring was increased the cost difference would decrease by about 8% and that in general, the cost difference of treating one eye versus two eyes would decrease over time.

4.2.4.3 The Assessment Group performed one-way sensitivity analyses on the costs of blindness and found that the alternative assumptions derived from consultation responses were very similar to those used in the original Assessment Group report. The Assessment Group noted that some component assumptions of the costs of blindness – namely the proportion of people who are blind and receiving community care services – had an effect on the ICERs. When this proportion was assumed to be between 6% and 25%, the ICER decreased by between £1,700 and £3,000 per QALY gained for pegaptanib and by about £1,300 and £2,600 per QALY gained for ranibizumab (predominantly classic lesions compared with PDT and best supportive care) and by between £1,200 and £3,000 per QALY gained for ranibizumab (minimally classic and occult no classic lesions)...

4.2.4.4 The Assessment Group also explored the impact of alternative assumptions for the costs of administering intravitreal injections based on the Royal College of Ophthalmologists report 'Commissioning Contemporary AMD Services: a guide for commissioners and clinicians' (2007). The results showed that the costs given by the Royal College of Ophthalmologists were higher than the day-case costs identified by the Assessment Group. The effect of the Royal College costs on the ICERs depended on the number of injections assumed. For ranibizumab, the ICER declined from baseline when 5.6 injections per year were assumed, and increased when 12 injections per year were assumed. When the lowest numbers of injections were assumed for predominantly classic lesions compared with PDT the ICER decreased by about £15,400 and by about £9,400 compared with best supportive care. The ICER decreased by £16,000 for minimally classic lesions. For pegaptanib, the ICERs generally increased by between £2500 and £6000 per QALY gained from the day-case procedure base case depending on the number of injections and assuming a disease-modifying effect in year 3 only. When the costs of administering the injection were assumed to be 75% outpatient and 25% inpatient, the ICER for pegaptanib decreased by about £4,000 per QALY and that of ranibizumab by between £1,600 and £2,600 per QALY gained depending on lesion type.

4.2.4.5 The Assessment Group also explored the impact of using alternative assumptions for utilities from those used in its base case (Brown). These included utilities elicited using the time trade-off technique elicited from people without AMD wearing contact lenses that simulated the vision experienced by AMD patients (Brazier), and another set of utilities using the HUI3 instrument. When the Brazier utilities were used, the ICER for pegaptanib increased by about £8000 per QALY gained and for ranibizumab by between £3000 and £7000 per QALY gained depending on lesion type.

When the HUI3 utilities were used the ICER for pegaptanib increased further by about £60,000 per QALY gained. For ranibizumab the ICER increased by between £20,000 and £32,000 per QALY gained depending on lesion type.

4.2.4.6 The Decision Support Unit's analysis of the manufacturer's model for pegaptanib reproduced the manufacturer's finding that pegaptanib treatment is more cost effective in subgroups with better baseline visual acuity. The most cost-effective subgroup included people with visual acuity between 6/12 and 6/24. When the inputs used in the Assessment Group's base case are applied in the manufacturer's model, assuming a disease-modifying effect in year 3 only, the ICER was £38,700 per QALY gained in the whole group, and £25,500 per QALY gained in the 6/12 to 6/24 subgroup. When the Royal College of Ophthalmologists' costs for administering injections and the Brazier utilities were assumed the ICER was £27,200 per QALY gained in the 6/12 to 6/24 subgroup. However, this figure assumed a lifetime disease-modifying effect, rather than up to year 3 only. When the HUI3 utilities were assumed the ICER further increased to about £58,000 per QALY gained in this subgroup of patients with a lifetime disease-modifying effect.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of ranibizumab and pegaptanib for the treatment of wet AMD, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by people with wet AMD, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee considered the clinical effectiveness evidence. It discussed the results for loss of fewer than 15 letters of visual

acuity, which was the primary outcome of all the RCTs. It noted that the effect size was greater for all lesion types in the ranibizumab studies than in the pegaptanib studies. The Committee concluded that both pegaptanib and ranibizumab reduce loss of visual acuity compared with sham injection, and additionally for ranibizumab compared with PDT in patients with predominantly classic lesions.

4.3.3 The Committee discussed the RCT results for gain in visual acuity, recognising the importance of this to patients with AMD. It noted that there were differences in the RCT data for this endpoint between the two treatments. Thus in the ranibizumab trials, there was a substantial increase in the proportion of patients gaining 15 or more letters of visual acuity, whereas for pegaptanib relatively few patients gained 15 letters or more. The Committee also discussed the RCT results on mean change in visual acuity. Results showed that there were statistically significant net gains in visual acuity for ranibizumab whereas pegaptanib only reduced the loss of letters. The Committee concluded on the basis of the RCT evidence that ranibizumab is more clinically effective than pegaptanib in improving net visual acuity.

4.3.4 The Committee considered the licensed dosing regimen for ranibizumab compared with that used in the main RCTs. It understood that the rationale for the regimen in the marketing authorisation was based on evidence from a drug and disease model submitted by the manufacturer indicating that the beneficial effects of ranibizumab peak at 3 months after three injections, after which a plateau of effect is reached, and that continued monthly injections may not be necessary in all patients to maintain this benefit. However, it was concerned that the results of the PIER trial, in which injections were given less frequently to all patients after the third month, which is similar to the dosing regimen recommended in the marketing authorisation, showed ranibizumab to be less effective than in the MARINA and ANCHOR trials in

which 24 monthly injections were given. It noted the results of a further study, PrONTO, which suggested that clinical benefit may be maintained with a lower average number of injections per patient, if injections are given more or less frequently depending on visual acuity and optical coherence tomography measure of response. However, it noted that PrONTO was a small, uncontrolled study investigating only a subset of patients with wet AMD. The Committee concluded that there was some uncertainty about the need for a full course of 24 monthly injections in order to achieve the results seen in the MARINA and ANCHOR trials.

4.3.5 The Committee discussed the adverse events associated with the use of the anti-VEGF agents. The Committee heard from clinical specialists that ranibizumab and pegaptanib have broadly similar adverse-event profiles, that most adverse events are manageable and that serious ones are rare. However, the Committee was aware of the results in the SPC showing that the overall incidence of arterial thromboembolic events from the MARINA, ANCHOR and PIER trials was higher for patients treated with ranibizumab 0.5 mg (2.5%) compared with the control arm (1.1%).

4.3.6 The Committee considered whether the clinical effectiveness of anti-VEGFs varies by lesion type. It noted that, in the ranibizumab RCTs, patients who had predominantly classic lesion types had accrued similar benefits to patients with minimally classic and occult no classic lesion types after treatment. The clinical evidence on pegaptanib was not stratified by lesion type. The Committee heard that in clinical practice anti-VEGFs treatment results in similar effect across all lesion types. It heard from clinical experts that although the classification by lesion type is relevant to laser-based treatments where there is a need to delineate the margins of CNV, such classification is not relevant to the use of anti-VEGFs. The Committee concluded that anti-VEGF treatments were clinically effective across lesion types.

4.3.7 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 the correlation between baseline acuity and treatment effect to be clinically plausible.

4.3.8 The Committee discussed key assumptions affecting the cost effectiveness analysis of the treatments. These were the:

- duration of treatment
- frequency of injections of ranibizumab that would be required to maintain response in clinical practice
- extrapolation of treatment benefit associated with anti-VEGF treatment beyond the duration of the RCTs, including consideration of any disease-modifying effect
- utilities used in the economic model
- costs related to blindness (defined as visual acuity less than 6/60), including low-vision aids, visual rehabilitation and community care
- costs of adequate facilities and staffing for intravitreal injection
- cost effectiveness of anti-VEGF treatment in the first affected eye.

The Committee discussed the assumption of treatment duration being limited to 2 years. It understood that CNV may recur after cessation of treatment, and heard from some consultees that rapid deterioration of vision after treatment cessation is sometimes observed. It heard from clinical specialists that it is unclear how long treatment would be continued in practice, that there is an evolving evidence base, and 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.

4.3.9 The Committee also noted that for economic modelling of predominantly classic lesion types with ranibizumab, the Assessment Group model was based on only 1 year of treatment (in keeping with the ANCHOR study), while for ranibizumab in minimally classic and occult no classic lesions, and for pegaptanib for all lesion types, 2 years of treatment had been modelled (in keeping with the MARINA and VISION studies). The Committee believed that the scenario in which the Assessment Group had estimated the ICER for 2 years of treatment in predominantly classic lesions would be more appropriate, noting that the duration of treatment was not expected to vary by lesion type in clinical practice and could extend beyond 2 years (see sections 4.3.6 and 4.3.11).

4.3.10 The Committee discussed assumptions for the frequency of ranibizumab injection, bearing in mind the issues discussed in section 4.3.4. It noted the drug dosing model presented by the manufacturer that had been accepted by the European Medicines Agency (EMEA) as a basis for the regimen in the marketing authorisation. It noted that the model assumed that the individualised dosing would result in stable visual acuity for the majority of the patients, with a mean of 8 injections required in the first year followed by a mean of 6 injections in the second year. It noted, based on comments from clinical specialists and from consultees, including the Royal College of Ophthalmologists, that this was likely to be frequently borne out in practice. However, the Committee remained concerned about the assumption that the benefit achieved in the pivotal trials could be matched with lower doses.

4.3.11 Taking into account its considerations over the required frequency of ranibizumab injections (as in section 4.3.10) and that treatment may continue beyond 2 years for some patients (as in section 4.3.9), the Committee concluded that on balance it would be reasonable to consider an assumption of a total of 24 injections of ranibizumab. In other words the Committee considered that although 24 injections over 2 years may be an overestimate, the assumption that no-one would receive further injections after 2 years was not probable.

4.3.12 The Committee further noted that there was no evidence to ascertain how benefits would accrue in the long term if treatment is stopped after 2 years, as assumed in all three economic models. There is therefore great uncertainty in appraising the validity of extrapolations made in the models. The approach used in the Assessment Group model was to assume that benefits of treatment would gradually decline at the same rate as for the usual care cohort, although starting at a higher visual acuity – that is, retaining higher visual acuity levels over the control arm throughout the 10-year time horizon. The Committee concluded that this approach would be reasonable to accept as a basis for decision making.

4.3.13 The Committee also noted that for pegaptanib, evidence of a disease-modifying effect had been submitted. It accepted that such an effect was plausible, but not for a lifetime duration after treatment had stopped. It was persuaded that it was reasonable to infer that there was some disease-modifying effect for 3 years after stopping treatment. It therefore concluded that a disease-modifying effect could be assumed to slow disease progression for 3 years after stopping treatment but that thereafter progression was at the same rate as in the control arm.

4.3.14 The Committee discussed the utilities used in the models. It considered that it might have been more appropriate to use utilities

derived using a generic and validated classification system such as the EQ-5D, rather than those used in both the Assessment Group and the manufacturers' models. It noted that use of the EQ-5D results in a much smaller difference, perhaps by as much as a factor of four, between utilities reflecting the best and worst vision states in the economic models... It discussed the alternative utilities used in the manufacturer's model for ranibizumab (Brazier) derived using the time trade-off technique but from the general population. It also discussed utilities derived using the HUI3 instrument (Espallargues). The Committee noted that there could be advantages in using the HUI3 instrument because it was closer to the NICE reference case and because of its explicit inclusion of a vision modality. However, it was concerned about whether it captured the full variation in utilities between the different visual acuity states in patients. Overall the Committee concluded that the Brown utilities lay at one end of the plausible spectrum and that the Espallargues utilities lay at the other. The Committee was persuaded that the latter were too insensitive to acuity differences and that the Brazier utilities, which were much closer to the Brown end of the spectrum, provided a plausible range for utility assumptions.

4.3.15 The Committee discussed the assumptions about costs related to blindness (such as registration, low-vision aids and rehabilitation). It heard from consultees that the assumptions in the Assessment Group base case were low, if not for standard practice, then for best practice. The Committee considered sensitivity analyses using high uptake and high costs of blindness and noted that these resulted in significant reductions in the ICERs for both drugs. The Committee decided that it was unrealistic to assume the extreme high or low uptake rates and costs of blindness presented in the sensitivity analysis in the Assessment Report. In addition, the Committee considered that for those patients who retained good to

normal visual acuity in one eye, the absolute cost of 'blindness' – that is, to support them – would be proportionately lower than in those patients in whom both eyes were affected. Taking these factors into account, the Committee concluded that an appropriate assumption about the costs of blindness would lie between the Assessment Group base case and the combined high-uptake, high-cost scenario.

4.3.16 The Committee discussed the assumptions in the models for the costs of administering intravitreal injections. The Committee heard from clinical specialists that the costs of appropriate facilities and staffing for intravitreal injection were higher than had been assumed in the base case of the models. The Committee discussed basing the costings on a sensitivity analysis in which intravitreal injections were assumed to be given as a day case. The Committee noted the sensitivity analysis from the Assessment Group in which costs were based on the Royal College of Ophthalmologists' commissioning guidelines for provision and treatment of AMD with anti-VEGFs. The results of this extra work showed that the Royal College of Ophthalmology costs were even higher than the day-case costs. The Committee was persuaded that in practice, for the foreseeable future, a mixture of day-case and outpatient procedures would occur. It concluded that a reasonable approach, as suggested by one of the consultees, would be to assume 75% of the procedures at the cost of a day case and 25% at the cost of an outpatient appointment.

4.3.17 The Committee discussed whether it would be appropriate to consider recommending treatment in the better-seeing eye only. It noted all the concerns raised by consultees and understood that most consultees felt that it would be unacceptable, and clinically inappropriate, to treat only the second affected eye. It was persuaded that treating only the second eye could result in losing the opportunity to preserve vision because the second eye could be

affected by an untreatable cause of visual loss, or might not respond to treatment with anti-VEGFs. With all these issues in mind the Committee concluded that its considerations of cost effectiveness should relate to treating the first eye to present clinically.

4.3.18 The Committee discussed the cost effectiveness of treating the first eye affected by AMD even while good (albeit) monocular vision was available from an unaffected eye. Firstly it considered that patients' quality of life, although importantly affected by loss of binocular vision, is mainly driven by vision in the better-seeing eye. It noted one study in which the difference in utility between having 6/6 vision in both eyes, and having 6/6 vision in one eye but poor vision in the other, was approximately 0.1. This utility differential is substantially lower than that between very good and very poor vision in the better-seeing eye (approximately 0.4 or 0.5 if Brown or Brazier utilities are used). It noted, however, from consultees that there would be considerable anxiety and depression associated with allowing an eye known to be affected with AMD to deteriorate without treatment, which may not be reflected in published utility studies.

4.3.19 The Committee discussed the proportion of patients who presented with AMD when only one eye was affected with the condition. It heard that about 70% of patients present with both eyes affected by AMD and that the standard approach is to treat the better-seeing eye. Of the 30% presenting with only one eye affected, it noted that about 10% per year (and 40% after 5 years) develop the disease in the second eye.

4.3.20 A policy of treating the first eye to come to clinical attention would result in substantially higher costs, but fewer savings and lower utility gains, than a policy of only treating the better-seeing affected eye. The Committee estimated (based on 30% of treatment yielding

a reduced QALY gain) an expected cost per QALY for a first-eye strategy about 50% higher than that for treating the better-seeing affected eye only. It concluded that the ICERs, assuming a strategy of treating the first affected eye with either ranibizumab or pegaptanib, would not fall within a range considered to be a cost-effective use of NHS resources.

4.3.21 The Committee discussed the number of injections of ranibizumab assumed in the model. It noted that if 8 injections would be required in the first year and 6 in the second, as suggested by consultees (see section 4.3.10), ICERs would be substantially lowered. However, it considered that many patients would be likely to require more injections than this to maintain benefit. The Committee discussed a suggestion by the manufacturer in their response to consultation that the number of ranibizumab injections paid for by the NHS could be capped, with any remaining injections paid for by the manufacturer. 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. It 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.

4.3.22 The Committee then reconsidered the economic modelling undertaken for pegaptanib, making the additional assumption that pegaptanib had a plausible continued disease-modifying effect 2 years after treatment discontinuation. The ICER from the Assessment Group model of £47,800 per QALY, based on assuming day-case injection costs, reduced to £42,000 per QALY when a 3-year the disease-modifying effect was factored in. It noted that the manufacturer's model produced lower ICERs based

on similar cost assumptions. However, it did not accept the assumption in the manufacturer's model that the post-treatment effect, estimated in the first year following discontinuation of treatment, can be applied for all subsequent years. The Committee further noted there could be differential gains for different subgroups of patients according to their starting visual acuity. It noted that focusing on the most responsive subgroup resulted in lower ICERs. For all other scenarios the cost effectiveness was even less favourable. However, the Committee estimated that even with the reduced costs from assuming that 25% of treatments are administered in outpatients and with the higher costs of blindness, the ICER for pegaptanib for treating the first or both eyes over best supportive care would be outside the range it regarded as an appropriate use of NHS resources. As in the case of ranibizumab, this estimate reflected the use of Brazier utilities and a policy of treating the first-affected eye.

4.3.23 The Committee discussed criteria for starting therapy with anti-VEGF treatments. It was in agreement in general with the criteria set out in the clinical trials for both drugs in terms of best-corrected visual acuity, no permanent structural damage to the central fovea, the lesion size being less than or equal to 12 disc areas in greatest linear dimension and that there is evidence of recent presumed disease progression as shown by blood vessel growth or visual acuity changes. The Committee was aware that to ensure the presence of wet AMD, it was essential that these criteria were adhered to. The Committee also concluded that corrected visual acuity of 6/60 was an appropriate level for treatment as the majority of the trial participants had visual acuity above 6/60, and 6/60 is the level where a person is considered to be legally blind in the UK...

4.3.24 In summary, the Committee concluded that both pegaptanib and ranibizumab are clinically effective in the treatment of wet AMD, but that ranibizumab is associated with greater clinical benefit. It

concluded that treatment with ranibizumab of the first-affected eye would be cost effective if the manufacturer pays for the costs of treatment beyond 14 injections in the treated eye. It further concluded that treatment of wet AMD with pegaptanib is not within a plausible range that could be considered a cost effective use of NHS resources.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX).

6 Proposed recommendations for further research

6.1 The Appraisal Committee considered that further research into the effectiveness of anti-VEGFs in wet AMD could include studies:

- about the cost effectiveness of ranibizumab compared with bevacizumab
- to investigate the long-term effects of anti-VEGFs in patients with AMD, including effects on visual acuity, anatomical damage to the macula, quality of life and adverse events
- to establish the appropriate duration and optimal treatment regimen in terms of frequency of injections

7 Related NICE guidance

NICE has issued the following related guidance.

Guidance on the use of photodynamic therapy for age-related macular degeneration. NICE technology appraisal 68 (September 2003). Available from: www.nice.org.uk/TA068

8 Proposed date for review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 It is proposed that the guidance on this technology is considered for review in December 2010. The Institute would particularly welcome comment on this proposed date.

Andrew Stevens
Chair, Appraisal Committee
December 2007

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor David Barnett (Vice-Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Chesterfield PCT

Mr Brian Buckley

Chair, Incontact

Dr Carol Campbell

Senior Lecturer, University of Teesside

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Ms Jude Cohen

Special Projects Consultant, UK Council for Psychotherapy

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic Ltd

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, Nottingham University

Mrs Eleanor Grey

Lay representative

Dr Catherine Jackson

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

Dr Peter Jackson

Clinical Pharmacologist, Sheffield Teaching Hospitals NHS Foundation Trust.

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Dr Damien Longson

Consultant in Liaison Psychiatry, Manchester Mental Health & Social Care Trust

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Katherine Payne

Health Economics Research Fellow, The University of Manchester

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag Ltd

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

Senior Lecturer, Department of Primary Care and General Practice

B. NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical advisor and a project manager.

David Chandiwana
Technical Lead

Helen Chung
Technical Adviser

Chris Feinmann
Project Manager

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Southampton Health Technology Assessment Centre, University of Southampton.

- Colquitt, J.L. et al. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation. November, 2006.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Novartis Pharmaceuticals Ltd (ranibizumab)
- Pfizer (pegaptanib)

II Professional/specialist and patient/carer groups:

- Age Concern England
- College of Optometrists
- Counsel and Care for the Elderly
- Department of Health
- Macular Disease Society
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal National Institute of the Blind
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Medicines and Healthcare Products Regulatory Agency (MHRA)
- NHS Quality Improvement Scotland
- Novartis
- Institute of Ophthalmology, University College London
- NCCHTA
- Southampton Health Technology Assessment Centre (SHTAC)
- National Collaborating Centre Acute Care

C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on ranibizumab and pegaptanib by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Professor Simon Harding, Consultant Ophthalmologist, nominated by the Royal College of Ophthalmologists – clinical specialist.
- Professor Andrew Lotery, Professor of Ophthalmology, nominated by the Royal National Institute for the Blind – clinical specialist.
- Barbara McLaughlan, Eye Health Campaigns Manager, nominated by the Royal Institute for the Blind – patient expert.
- Mrs Lydia Willie, nominated by the Royal Institute for the Blind – patient expert.