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Ranibizumab and pegaptanib for the treatment of age-related macular degeneration

NICE technology appraisal guidance 155

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration

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- Information for people with wet age-related macular degeneration and their carers ('Understanding NICE guidance').
- Details of all the evidence that was looked at and other background information.

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1 Guidance

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

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

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

1.2 It is recommended that treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. It is recommended that a national protocol specifying criteria for discontinuation is developed.

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

1.4 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, dry and wet AMD. Dry AMD (non-neovascular) is a form of extensive atrophy (wasting) of cells that progresses slowly, whereas the wet form can lead to a rapid worsening of vision. 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. A protein known as vascular endothelial growth factor (VEGF), which induces new blood vessel formation (angiogenesis), vascular permeability and inflammation, has been implicated in the development and progression of CNV. CNV can be subdivided into classic and occult forms according to its appearance on investigation by fluorescein angiography. A mixture of classic and occult CNV can occur in the same lesion. CNV can also be described in terms of its location: the fovea is the central part of the macula, and CNV that develops below the foveal area is termed 'subfoveal CNV'.
- 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. 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 only see from a distance of 6 metres or less what someone with normal vision can see from 60 metres away. 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. More recently, drugs that inhibit the action of VEGF have been developed for the treatment of wet AMD.

3 The technologies

Ranibizumab

- 3.1 Ranibizumab (Lucentis, Novartis) is a humanised therapeutic antibody fragment that binds to VEGF-A isoforms of VEGF thereby preventing binding of VEGF-A to receptors VEGFR-1 and VEGFR-2.
- 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) during this maintenance phase, a further

dose of ranibizumab should be administered. The interval between two doses should not be shorter than 1 month.

- 3.3 The summary of product characteristics (SPC) states that adverse events commonly associated with ranibizumab include conjunctival haemorrhage, eye pain, vitreous floaters, retinal haemorrhage, increased intraocular pressure, vitreous detachment, intraocular inflammation, eye irritation, cataract, foreign body sensation in the eyes, visual disturbance, blepharitis, subretinal fibrosis, ocular hyperaemia, blurred/decreased visual acuity, dry eye and vitreitis. For full details of side effects and contraindications, see the SPC.
- 3.4 The cost of a ranibizumab injection is £761.20 (excluding VAT; British national formulary [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) is a pegylated modified oligonucleotide that binds to VEGF-165 and inhibits 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 6 weeks (9 injections per year) by intravitreal injection into the affected eye.
- 3.7 The SPC states that adverse events commonly associated with pegaptanib are anterior chamber inflammation, eye pain, increased intraocular pressure, punctate keratitis, vitreous floaters and vitreous opacities. 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 four randomised controlled trials (RCTs) of ranibizumab and two RCTs of pegaptanib. Outcomes measured in the RCTs included changes in visual acuity (loss, maintenance, gain, mean change and deterioration to visual acuity 3/60 [in the UK, 3/60 is the level of visual acuity at which patients are registered blind]), anatomical changes in CNV lesions, visual function questionnaire scores, contrast sensitivity and adverse events.

Ranibizumab

- 4.1.2 Four RCTs of ranibizumab (MARINA [minimally classic lesions; ranibizumab versus sham injection], ANCHOR [predominantly classic lesions; ranibizumab versus sham plus PDT], PIER [all lesions; ranibizumab versus sham injection] and FOCUS [predominantly and minimally classic lesions; ranibizumab plus PDT versus sham plus PDT]) 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 (unlicensed) and 0.5 mg (licensed). 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 Loss of fewer than 15 letters of visual acuity was the primary endpoint in the studies. From baseline to 12 months, statistically significantly more patients receiving 0.5 mg ranibizumab lost fewer than 15 letters of visual acuity compared with both sham injection (94.6% compared with 62.2%, MARINA study) and PDT (96.4% compared with 64.3%, ANCHOR study). In the PIER study, 90.2% of the 0.5 mg ranibizumab group lost fewer than 15 letters compared with 49.2% in the sham group ($p < 0.0001$).
- 4.1.4 Gain in visual acuity was a secondary endpoint in the studies. 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 ($p = 0.0033$).
- 4.1.5 The MARINA, ANCHOR and FOCUS trials all reported mean increases in visual acuity in the 0.5 mg ranibizumab group compared with baseline. The FOCUS trial reported mean gains in letters of 4.9 (0.5 mg ranibizumab plus PDT group) compared with mean losses of 8.2 letters in the sham plus PDT group. The ANCHOR study (0.5 mg ranibizumab group) reported mean gains of 11.3 letters compared with a loss of 9.5 letters in the sham plus PDT group. In the MARINA trial, mean gains in letters were 7.2 and 6.6 at 12 and 24 months, respectively, and the corresponding mean losses in the sham group were 10.4 and 14.9 letters at 12 and

24 months respectively. These results were statistically significant in all the trials.

- 4.1.6 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 compared with 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%). However, in the second year of the MARINA study, the rate of arterial thromboembolic events was similar in patients treated with ranibizumab 0.5 mg (2.6%) compared with patients in the control arm (3.2%).

Pegaptanib

- 4.1.7 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 (licensed), 1.0 mg (unlicensed) and 3.0 mg (unlicensed) 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.
- 4.1.8 Loss of fewer than 15 letters of visual acuity was the primary endpoint in the VISION study. Statistically significantly more patients (70%) receiving 0.3 mg (the licensed dose) pegaptanib compared with sham injection (55%) 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 the

sham injection group (12%; $p = 0.004$). 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 ($p = 0.02$). In the 0.3 mg group 6% of patients gained more than 15 letters compared with 2% in the sham group.

- 4.1.9 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.
- 4.1.10 The VISION study reported that the proportion of people losing at least 15 letters of visual acuity from baseline after 2 years was lower for patients who stopped pegaptanib (at the licensed dose) after 1 year compared with those who had never received pegaptanib (relative risk 0.68, 95% confidence interval [CI] 0.51 to 0.90, $p = 0.008$). The manufacturer interpreted this as demonstrating a disease-modifying effect; if the treatment effect was exclusively symptomatic, the visual acuity of patients who discontinued treatment after 1 year would have quickly returned to that seen in the sham injection group, rather than remaining significantly better a year after stopping treatment, as observed in the study. The Assessment Group considered this to be biologically plausible because anti-VEGF drugs target the underlying pathology in AMD. However the Assessment Group also noted uncertainty in this conclusion because the decline in the proportion of people losing fewer than 15 letters from 54 weeks to 102 weeks in the VISION study was the same for patients who received pegaptanib as for those who had never received the drug (14%).
- 4.1.11 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 in patients in the sham injection group than in those in the 0.3 mg pegaptanib group, suggesting that the preparation procedure itself (which included an ocular antiseptis 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 cost-utility models. Both models were Markov state transition models, with the states being different levels of visual acuity and death. Both models assumed that only the better-seeing eye is treated. The models were based on 1 or 2 year data from randomised controlled trials, after which there was extrapolation, based on the life expectancy of the cohort, to a 10-year time horizon. Input assumptions were determined from an NHS and personal social services perspective. There was no comparison, direct or indirect, of ranibizumab and pegaptanib with each other.

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 RCTs (ANCHOR for comparison with PDT in predominantly classic lesions, MARINA for comparison with best supportive care in minimally classic lesions and PIER for reduced-frequency dosage in all lesion types). 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 a study (TAP) in which PDT was compared with best supportive care.

- 4.2.2.3 The model had five health states defined by declining visual acuity ranging from 6/15 or better (least severe) to less than 3/60 (most severe), and an additional absorbing state, death. The manufacturer's model 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 1 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.
- 4.2.2.4 The utility values used in the model were based on a study in which outcomes were assessed in members of the general UK population (n = 108) who experienced simulated AMD vision states using custom-made lenses. The study included a preference-based measure (HUI-3), selected questions from a visual function questionnaire and time-trade-off (TTO) by direct elicitation (Brazier study). The utility values derived using TTO by direct elicitation were stated to have a strong relationship with visual acuity and these were the utility values used in the model. The difference in mean values between the lowest and highest visual acuity groups

was 0.367 (0.497 in the group with a visual acuity of less than 3/60 and 0.864 in the group with a visual acuity of 6/15 or better). These values were based on impaired vision in both eyes. However, the manufacturer argued that the relative benefits of binocular and monocular vision should be taken into account, citing a study which showed a difference in utility value of approximately 0.1 between people with good visual acuity in both eyes and people with good vision in only one eye. The manufacturer's submission also discussed utility values derived using the HUI-3 instrument (Espallargues). In this study, a utility difference of 0.02 between people with visual acuity ranging from 6/12 to 6/24 (utility value of 0.38) and people with visual acuity ranging from 6/24 to 3/60 (utility value of 0.36) was reported.

- 4.2.2.5 The base-case incremental cost-effectiveness ratios (ICERs) for predominantly classic lesions, assuming 1 year of treatment as per the ANCHOR RCT, were £4489 per quality-adjusted life-year (QALY) gained for ranibizumab versus PDT, and £14,781 per QALY gained for ranibizumab versus best supportive care. For occult no classic lesions, assuming 2 years of treatment, the ICER was £26,454 per QALY gained for ranibizumab versus best supportive care. Likewise, for minimally classic lesions, the ICER was £25,796 per QALY gained. For all lesion types (PIER), assuming 1 year of treatment, the ICER was £12,050 per QALY gained.

Pegaptanib

- 4.2.2.6 The manufacturer's model for pegaptanib compared the cost effectiveness of pegaptanib 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. The base-case analysis is based on all lesion types. The analysis was based on patient-level data from the VISION study.

- 4.2.2.7 The model had 12 health states, defined by visual acuity ranging from 6/10 or better to less than 3/60, and an additional absorbing state, death. Treatment was assumed to be 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.
- 4.2.2.8 The utility values used in the model were based on a study of health-related quality of life in AMD patients (Brown study, n = 80). The utility values were derived by direct elicitation using both the standard gamble and TTO methods. In multivariate linear regression analysis, the TTO method produced a higher correlation with visual acuity than the standard gamble approach. The difference in mean TTO values between the lowest and highest visual acuity groups was 0.49 (0.40 in the group with a visual acuity of less than 3/60 and 0.89 in the group with a visual acuity of 6/12 or better).
- 4.2.2.9 In the base case, the ICER was £15,819 per QALY gained for scenario A and £14,202 per QALY gained 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.

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). The transitions between states in the model were based on RCT data, noting that the endpoints in the RCTs fell broadly into three clinically accepted endpoints; loss of less than 15 letters, intermediate vision

loss (loss of 15–30 letters) and severe vision loss (loss of more than 30 letters). The estimated impact of these changes in visual acuity on the cost effectiveness of ranibizumab and pegaptanib was estimated using a Markov state transition model. The model assumes that only the better-seeing eye is treated.

4.2.3.2 A six-state Markov model was developed and the rate of disease progression was modelled 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 (or 1 year for ranibizumab in predominantly classic lesions) to 10 years in both arms of the model. Ranibizumab and pegaptanib treatments are assumed to have stopped at the end of year 2, and thereafter 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 Where possible, the Assessment Group used routinely available unit cost estimates, that is NHS reference costs and unit costs of community care, in its economic analyses. Resources and costs incorporated in the Assessment Group model included those for treatment, administration, monitoring, managing adverse events and blindness. Costs related to blindness included the administrative cost of registering as blind or partially sighted, and the cost of low vision aids, low vision rehabilitation, community care, residential care, treatment of depression and hip replacement. In the base case it was assumed that all injections would be carried out as outpatient procedures at a unit cost of £90.20. In sensitivity analyses, it was assumed that all injections would be carried out as day-case procedures at a unit cost of £395, or that the cost of administering the injection would be a mix of day case (75%) and outpatient (25%) costs.

4.2.3.4 Health state utility values derived using TTO by direct elicitation from patients with AMD (Brown study, n = 80, see section 4.2.2.8) were used because the Assessment Group considered these to be

the most credible published utility values for visual loss associated with AMD.

Ranibizumab

- 4.2.3.5 The Assessment Group's base-case ICERs over a 10-year time horizon for predominantly classic lesions assuming 1 year of treatment were £15,638 per QALY gained compared with PDT, and £11,412 per QALY gained compared with best supportive care. For minimally classic lesions and occult no classic lesions, assuming 2 years of treatment, they were £25,098 per QALY gained compared with best supportive care.
- 4.2.3.6 The Assessment Group carried out sensitivity analyses of different assumptions used in their model. The results for ranibizumab showed that as the time horizon decreased the ICERs increased.
- 4.2.3.7 In one-way sensitivity analyses, for predominantly classic lesions, reducing the number of injections from 12 to 9 in the first year of treatment reduced the ICER from £15,638 to £6,897 per QALY gained compared with PDT and from £11,412 to £6,087 per QALY gained compared with best supportive care. For patients with minimally classic and occult no classic lesions, with a treatment duration of 2 years (as per the MARINA trial protocol), 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) reduced the ICER considerably from £25,098 to £12,649 per QALY gained compared with best supportive care. In these analyses, it was assumed that the QALY gain would not differ with changes in the number of injections.
- 4.2.3.8 In one-way sensitivity analyses in which the injections were costed as day-case rather than outpatient procedures, the ICERs increased. The ICER increased from £15,638 to £26,102 per QALY gained compared with PDT and from £11,412 to £17,787 per QALY gained compared with best supportive care. For patients with

minimally classic and occult no classic lesions, the ICER increased from £25,098 to £35,157 per QALY gained compared with best supportive care.

- 4.2.3.9 The cost-effectiveness estimates were 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 resulted in ranibizumab being economically 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 were used in one-way sensitivity analyses, the ICERs increased from £15,638 to £19,967 per QALY gained for predominantly classic lesions compared with PDT, and from £11,412 to £16,281 per QALY gained for predominantly classic lesions compared with best supportive care. For minimally classic lesions, the ICER increased from £25,098 to £29,446 per QALY gained.
- 4.2.3.10 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.
- 4.2.3.11 In probabilistic sensitivity analyses using the base-case assumptions, for patients with predominantly classic lesions compared with PDT, ranibizumab had a probability of being cost effective of 72% at a willingness to pay of £20,000 per QALY gained and 97% at a willingness to pay of £30,000 per QALY gained. For patients with predominantly classic lesions compared with best supportive care, ranibizumab had a probability of being cost effective of 95% at a willingness to pay of £20,000 per QALY gained

and 99% at a willingness to pay of £30,000 per QALY gained. For patients with minimally classic and occult no classic lesions, for the base-case analysis ranibizumab had a probability of being cost effective (compared with best supportive care) of 15% at a willingness to pay threshold of £20,000 per QALY gained and 81% at a willingness to pay threshold of £30,000 per QALY gained.

Pegaptanib

- 4.2.3.12 The Assessment Group estimated the base-case ICER for pegaptanib (all lesion types) compared with usual care to be £30,986 per QALY gained over a 10-year time horizon.
- 4.2.3.13 The Assessment Group carried out sensitivity analyses of different assumptions used in their model. As with ranibizumab, the results for pegaptanib showed that decreasing the time horizon increased the ICERs. The ICER was also sensitive to 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. Using high uptake and high unit-cost estimates resulted in pegaptanib being economically dominant (with a lower cost and better outcome) compared with usual care. However, when low costs and medium uptake assumptions were used, the ICER increased from the base case of £30,986 to £37,154 per QALY gained.
- 4.2.3.14 In another sensitivity analysis, a higher cost was assumed for providing all injections as a day-case procedure and the ICER for pegaptanib increased from the base case of £30,986 to £47,845 per QALY gained compared with best supportive care.
- 4.2.3.15 The Assessment Group also performed a sensitivity analysis to explore the assumption of a potential disease-modifying effect of pegaptanib. This relative risk reduction (see section 4.1.10) 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. When this relative risk reduction was applied to the Assessment Group model in year 3 (that is, for one year following cessation of treatment), the ICER decreased from £47,845 (using the day-case injection cost assumption, see 4.2.3.14) to £42,198 per QALY gained compared with best supportive care.

4.2.3.16 When the distribution of initial visual acuity was varied in sensitivity analyses, a cohort equally split between the 6/12–6/24 and 6/24–6/60 states produced an ICER of £35,913 per QALY gained, while a cohort with initial visual acuity of 6/24–6/60 produced an ICER of £46,285 per QALY gained compared with best supportive care.

4.2.3.17 In probabilistic sensitivity analyses using the base-case assumptions, pegaptanib had a probability of being cost effective (compared with usual care) of 17% at a willingness to pay of £20,000 per QALY gained and 58% at a willingness to pay of £30,000 per QALY gained using the base-case assumptions.

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

4.2.4.1 After considering the 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 of ranibizumab, and the utility values used in the analysis. The Decision Support Unit provided similar analyses using 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 explored the cost of treating the first eye to come to clinical attention rather than treating only the better-seeing

eye. The analysis assumed an annual incidence of AMD in the second eye of 10% and explored a number of different scenarios. It found that for ranibizumab the additional cost of treating two eyes ranged from about £9,900 to about £28,600, depending on the number of injections (9 to 24) over 2 years. For pegaptanib, the additional cost of treating two eyes ranged from about £9,100 to about £15,700.

- 4.2.4.3 In one-way sensitivity analyses on the costs of blindness, the Assessment Group 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 the level of uptake of community services (that is, the proportion of people who are blind and receiving community care services) had a much greater effect on the ICERs than other components of the costs of blindness. Therefore sensitivity analyses focused on varying this proportion from 6% to 17% or 25%.
- 4.2.4.4 In a one-way sensitivity analysis the Assessment Group used alternative utility values to its base case. This was a set of utility values estimated to be equivalent to those derived in the Brazier study, but adapted for the visual acuity states in the Assessment Group model (which were slightly different from those in the Brazier study). The difference in mean values between the lowest and highest visual acuity groups was 0.382 (0.518 in the group with a visual acuity of less than 3/60 and 0.900 in the group with a visual acuity of 6/12 or better).
- 4.2.4.5 The Assessment Group also explored the cumulative impact on the ICER of the following assumptions, which were preferred by the Committee to the original base case: alternative utility values (Brazier study), splitting the cost of administering the injection between day-case (75%) and outpatient (25%) costs and higher uptake of community care services (from 6% to 17% or 25%). When

the Brazier utilities were used, the ICER for ranibizumab for predominantly classic lesions increased from the base case of £15,638 to £19,491 per QALY gained compared with PDT, and from the base case of £11,412 to £14,388 per QALY gained compared with best supportive care; for minimally classic and occult no classic lesions the ICER increased from the base case of £25,098 to £31,966 per QALY gained compared with best supportive care. When the costs of administering the injection were split between day-case (75%) and outpatient (25%) costs, the ICER for ranibizumab for predominantly classic lesions was £29,272 per QALY gained compared with PDT and £20,416 per QALY gained compared with best supportive care; for minimally classic lesions the ICER was £41,575 per QALY gained compared with best supportive care. In addition, when the uptake of community care was assumed to increase from 6% (base case) to 25%, the ICER for ranibizumab for predominantly classic lesions decreased to £26,425 per QALY gained compared with PDT, and to £17,175 per QALY gained compared with best supportive care; for minimally classic lesions the ICER was £38,659 per QALY gained compared with best supportive care.

4.2.4.6 The Assessment Group also explored the cost effectiveness of ranibizumab in predominantly classic lesions assuming two years of treatment, whereas previously one year of treatment was assumed. Assuming 12 injections in each year, this increased the ICERs from the cumulative scenario described in section 4.2.4.5 from £26,425 to £37,489 per QALY gained for ranibizumab compared with PDT, and from £17,175 to £23,887 per QALY gained for ranibizumab compared with best supportive care.

4.2.4.7 Finally, in addition to the cumulative assumptions described in sections 4.2.4.5 and 4.2.4.6, but instead assuming that only 14 injections would be required over two years to attain the same clinical benefit without reducing the frequency of monitoring costs,

the ICER for ranibizumab for predominantly classic lesions further decreased from £37,489 to £13,671 per QALY gained compared with PDT, and from £23,887 to £9,900 per QALY gained compared with best supportive care. For minimally classic or classic no occult lesions the ICER decreased from £38,659 to £19,904 per QALY gained compared with best supportive care.

- 4.2.4.8 For pegaptanib, the Decision Support Unit used the manufacturer's model to reproduce the manufacturer's finding that the cost per QALY gained for pegaptanib treatment is lower in subgroups with better baseline visual acuity using all the Committee's preferred assumptions. The lowest cost per QALY gained was obtained in a subgroup of people with visual acuity between 6/12 and 6/24. When the inputs outlined in section 4.2.4.4 were cumulatively considered in the manufacturer's model, the ICER was £23,124 per QALY gained in the 6/12 to 6/24 subgroup compared with best supportive care, £40,627 per QALY gained for the 6/24 to >6/60 subgroup, £115,244 per QALY gained for the 6/60 to >3/60 subgroup, and £34,602 per QALY gained for the whole cohort. Using the same set of assumptions, the ICER from the Assessment Group model was £44,259 per QALY gained for the whole group irrespective of visual acuity levels.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal 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 ranibizumab reduces loss of visual acuity 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 between ranibizumab and pegaptanib in the RCT data for this endpoint. 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 compared with control. The Committee also discussed the RCT results on mean change in visual acuity, reported as the mean number of letters lost or gained in the treatment groups compared with the control arms. Results showed that there were statistically significant mean gains of letters for ranibizumab whereas pegaptanib reduced only the mean loss of letters. The Committee concluded on the basis of the RCT evidence that ranibizumab is more clinically effective than pegaptanib in improving 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 after three injections at 3 months, after which a plateau of effect is reached, and that continued monthly injections may not be necessary in all patients to maintain this benefit. It was concerned that the results of the PIER trial, in which injections were given less frequently (3-monthly) to all patients after the third month, showed ranibizumab to be less effective than in the

MARINA and ANCHOR trials in which monthly injections (24) were given. The Committee 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 on a measure of response on optical coherence tomography (a regimen similar to that in the marketing authorisation). 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 number and frequency of injections required 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. The Committee considered the data listed under 'undesirable effects' in the SPC showed that the overall incidence of arterial thromboembolic events from the MARINA, ANCHOR and PIER trials was higher for patients treated with ranibizumab compared with the control group, but that in the second year of the MARINA study the rate of arterial thromboembolic events was similar in patients treated with ranibizumab and patients in the control arm. The Committee concluded that ranibizumab and pegaptanib have broadly similar adverse-event profiles; most adverse events are manageable and serious ones are rare. It noted that the costs of adverse events were included in the Assessment Group model.
- 4.3.6 The Committee considered whether the clinical effectiveness of the two anti-VEGFs (ranibizumab and pegaptanib) varied by lesion type. It noted that, in the ranibizumab RCTs, the effects in patients who had predominantly classic lesion types were similar to those in

patients with minimally classic and occult no classic lesion types. The Committee heard that in clinical practice anti-VEGF treatment results in similar effects across all lesion types. It heard from clinical specialists 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 varied between subgroups defined according to baseline visual acuity. It noted that in the Assessment Group's model, treatment effect and rate of deterioration of vision were assumed to be independent of baseline visual acuity, but the model submitted by the manufacturer of pegaptanib assumed greater clinical benefits to be associated with better baseline vision. The Committee considered it to be plausible that people with better pre-treatment visual acuity are likely to benefit more from treatment than those with lower pre-treatment visual acuity. This could be, for example, because wet AMD lesions that have caused greater deterioration in visual acuity are also more likely to have caused permanent structural damage, which reduces response to anti-VEGF treatment.

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
- utility values used in the economic model

- costs related to blindness (defined as visual acuity less than 6/60 for those registered as partially sighted and 3/60 for those registered as blind), 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.

4.3.9 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 was sometimes observed. It heard from clinical specialists that it was unclear how long treatment would be continued in practice, that there was 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.

4.3.10 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 4.3.9).

- 4.3.11 The Committee discussed assumptions for the frequency of ranibizumab injection, bearing in mind the issues discussed in section 4.3.4. It noted that the drug dosing model presented by the manufacturer had been accepted by the European Medicines Agency (EMA) 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 such a dosing model 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 if injections were less frequent.
- 4.3.12 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.
- 4.3.13 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.

- 4.3.14 The Committee also noted that a disease-modifying effect had been suggested for pegaptanib. 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 effect for a year after stopping treatment. It therefore concluded that pegaptanib could be assumed to slow disease progression for a year after stopping treatment with the drug, but that thereafter progression was at the same rate as in the control arm.
- 4.3.15 The Committee discussed the utility values used in the models. It noted that the Assessment Group and the manufacturer for pegaptanib used utilities derived from AMD patients (Brown study), whilst the manufacturer for ranibizumab used utilities derived from the general population (Brazier study). Both sets of utility values had been derived using TTO direct elicitation. The Committee considered that in principle it is more appropriate to use utility values derived using a standardised and validated generic (non-disease-specific) instrument, such as the EQ-5D or HUI-3. It noted the utility values derived using HUI-3 (Espallargues) which reported a utility difference of 0.02 between two health states with markedly different visual acuities. The Committee agreed that this measure may therefore not fully capture the impact of AMD on patients' quality of life. The Committee concluded that on balance, the Brazier utility values provided the most plausible set of utility values for use in the economic models.
- 4.3.16 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 in the assessment report 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 accept 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' 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.

- 4.3.17 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 (NHS reference cost of £90.20 for an outpatient procedure) because provision had to be made for sterile conditions. It noted an analysis based on the NHS reference cost of £395 for a day-case procedure. The Committee also considered an additional analysis in which the Assessment Group estimated costs based on the Royal College of Ophthalmologists' commissioning guidelines for provision and treatment of AMD with anti-VEGFs. This analysis showed that the costs based on the Royal College of Ophthalmologists' guidelines were higher than for day-case procedures. The Committee considered the conflicting information available on the cost of administering intravitreal injections, and was persuaded by comments received during consultation that in practice, for the foreseeable future, a mixture of day-case and outpatient procedures would occur. It concluded that a reasonable approach would be to assume that the costs of administering

intravitreal injections were equivalent to a mix of 75% of the cost of a day case procedure and 25% of the cost of an outpatient procedure.

- 4.3.18 The Committee discussed whether it would be appropriate to consider recommending treatment in the better-seeing eye only: that is, not to treat where patients present with only one eye affected. It noted the concerns raised by consultees and understood that most consultees felt that it would be unacceptable, and clinically inappropriate, not to treat the first eye that comes to clinical attention. It was persuaded that any other scenario could result in losing the opportunity to preserve vision because the untreated better-seeing eye could subsequently be affected by an untreatable cause of vision 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 starting treatment with the first eye to present clinically.
- 4.3.19 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 noted that patients' quality of life was strongly correlated with, and mainly driven by, vision in the better-seeing eye. The Committee noted, however, that loss of normal binocular vision can result in a reduction in quality of life. It understood, for example, that there would be considerable anxiety and depression associated with allowing an eye known to be affected with AMD to deteriorate without treatment. It noted one study cited by the manufacturer of ranibizumab, in which the difference in utility between having 6/6 vision in both eyes, and having 6/6 vision in one eye but 6/12 or worse in the other eye, was approximately 0.1. The Committee noted that this utility difference was substantially smaller than that between very good and very poor vision in the better-seeing eye (approximately 0.4 or 0.5 if Brazier or Brown utility values are used,

respectively). Secondly, the Committee considered that for those patients who retained good to normal visual acuity in one eye, the savings in costs of 'blindness' would be considerably lower than in those patients with poor vision in both eyes.

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

4.3.21 The Committee noted that the economic modelling was carried out assuming that the better-seeing eye was treated. 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 that treatment for the first eye yields an 80% lower QALY gain than for treating the better-seeing eye. In addition there would be reduced savings on costs of blindness. Based on this the Committee agreed that an expected cost per QALY for a first-eye strategy would be about 50% higher than that for treating the better-seeing affected eye. It concluded that the ICERs for pegaptanib or ranibizumab would not fall within a range considered to be a cost-effective use of NHS resources using the assumptions outlined in 4.2.4.5 and 4.2.4.6 and assuming a strategy of treating the first-affected eye.

4.3.22 The Committee discussed the number of injections of ranibizumab assumed in the model. It noted that if 8 injections were required in the first year and 6 in the second, as suggested by consultees (see section 4.3.10), the ICERs for the different lesion types would be £13,671, £9,900 and £19,904 per QALY gained depending on

lesion type and comparator, as detailed in section 4.2.4.7. These figures assume that only the better-seeing eye is treated. Applying a 50% increase in these ICERs to include the treatment of the first eye, these ICERs would become approximately £20,500 and £14,800 per QALY gained in predominantly classic lesions compared with best supportive care and PDT respectively, and £29,900 in minimally classic or classic no occult lesions compared with best supportive care. However, the Committee considered that many patients would be likely to require more injections than this to maintain benefit. It discussed a proposal by the manufacturer in their response to consultation that the number of ranibizumab injections for which drug costs are paid by the NHS could be capped, with any remaining ranibizumab drug costs paid for by the manufacturer. 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. The Committee noted that these costs were not included in the modelling, but estimated that ranibizumab was likely to be cost effective if the cost to the NHS was limited such that the manufacturer pays for the drug cost of ranibizumab beyond 14 injections in the treated eye.

- 4.3.23 The Committee then reconsidered the economic modelling undertaken for pegaptanib compared with best supportive care after taking into account the following assumptions: disease-modifying effect up to 1 year after cessation of treatment ('year 3'), higher costs of blindness, costs of administering the injection as 75% day case and 25% outpatient, use of Brazier utility values, and 25% uptake of community care. In the Assessment Group model, this resulted in an ICER of £44,259 per QALY gained using a better-seeing eye strategy. Applying a 50% increase in these

ICERs to include the treatment of the first eye, this ICER would become approximately £66,400 per QALY gained. The Committee also noted that the manufacturer's model produced a lower ICER of £34,602 per QALY gained based on the same assumptions using a better-seeing eye strategy, corresponding to approximately £51,900 per QALY gained when there is a policy of treating the first eye to come to clinical attention.

4.3.24 The Committee further considered that there could be differential gains from pegaptinib for different subgroups of patients according to their starting visual acuity. The Committee considered the position of the different subgroups with reference to cost effectiveness and to whether there were any steps which the Committee should take to fulfil NICE's duties under the equalities legislation. It considered whether it would be appropriate to recommend pegaptanib for a specific subgroup. It noted that focusing on the most responsive subgroup resulted in lower ICERs. The Committee noted that, after considering all its preferred assumptions, the ICERs were: £23,124 per QALY gained for the 6/12 to 6/24 visual acuity subgroup; £40,627 per QALY gained for the 6/24 to >6/60 subgroup; and £115,244 for the 6/60 to >3/60 visual acuity subgroup. Applying a 50% increase in these ICERs to include the treatment of the first eye, these ICERs would become approximately £34,700, £60,900 and £172,900 per QALY gained respectively. The Committee thus concluded that for all visual acuity subgroups, pegaptanib was not a cost-effective use of NHS resources. It concluded that there was no impact on any particular group of patients that required particular action in order to comply with the Institute's obligations under the equalities legislation. The Committee noted that ranibizumab would be recommended as a treatment option for the whole of the patient group.

4.3.25 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 met. The Committee also considered when treatment should be recommended as an option in terms of baseline visual acuity. It noted that the population in the clinical evidence base had a corrected visual acuity between 6/12 and 6/96, and that there was no evidence from ranibizumab studies that would allow consideration of differences in clinical and cost effectiveness between subgroups with different baseline visual acuity. The Committee therefore concluded that it would be appropriate for treatment with ranibizumab to be recommended at a visual acuity range between 6/12 and 6/96.

- 4.3.26 The Committee discussed the issue of discontinuing therapy. It noted the lack of a formal clinical guideline in this area, but thought it was important that continuation of treatment be carefully considered by patients and their clinicians. It discussed suggestions from clinical specialists for criteria for defining a loss of adequate response and concluded that a clear protocol for discontinuation in people who have a loss of adequate response to therapy should be developed. It thought that such a protocol should specify criteria for discontinuation, which are likely to include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. The Committee thought that the most appropriate body to develop this protocol would be the Royal College of Ophthalmologists. Until such a protocol is developed it is recommended that locally agreed protocols be used. The Committee also noted that there could be a long gap between one

dose and the need for the next dose. It concluded that in this situation treatment should be considered as continuous regardless of whether a patient had been discharged from a clinic in between doses.

- 4.3.27 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 eye to be treated would be cost effective if the manufacturer pays for the drug cost of ranibizumab beyond 14 injections in the treated eye. The Committee further concluded that treatment with pegaptanib for wet AMD is not 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 that 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/TA155).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit support for monitoring local practice.

6 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

Published

Guidance on the use of photodynamic therapy for age-related macular degeneration. NICE technology appraisal 68 (2003). Available from:

www.nice.org.uk/TA068

8 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 The guidance on this technology will be considered for review in August 2011.

Andrew Dillon
Chief Executive
August 2008

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 Adviser 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, University of Birmingham

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 adviser 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 JL 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 (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 Blind People
- 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 non-manufacturer/sponsor consultees and commentators. 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 were also 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 of Blind People – clinical specialist.
- Barbara McLaughlan, Eye Health Campaigns Manager, nominated by the Royal Institute of Blind People – patient expert.
- Mrs Lydia Willie, nominated by the Royal Institute of Blind People – patient expert.