NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal Consultation Document

Ranibizumab and pegaptanib for age-related macular degeneration

1 Appraisal Committee's preliminary recommendations

1.1 Ranibizumab, within its marketing authorisation, is recommended for the treatment of wet age-related macular degeneration for people who have a confirmed diagnosis of predominantly classic subfoveal choroidal neovascularisation (CNV) (that is, the classic CNV component is 50% or more of the total lesion size), and only for the better-seeing eye, in the following circumstances.

- Their 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).

  Ranibizumab is not recommended for the treatment of people with minimally classic or occult lesions with no classic CNV (that is, the classic CNV component is less than 50% of the total lesion size).

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, or ranibizumab for minimally classic and occult lesions, 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 which 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. By definition the condition usually affects people who are

over 50 years old and the risk increases significantly with age. In the UK, the proportions of cases of wet AMD in each angiographic class are as follows: 20% predominantly classic (including ‘classic no occult’), 7% minimally classic and 73% ‘occult no classic’. 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 patients who have 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. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, 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 5 letters in visual acuity (Early Treatment Diabetic Retinopathy Study

[ETDRS] 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 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 (not yet in the 'British national formulary' [BNF]; NICE was notified of the price by the manufacturer. 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. VEGF is a secreted protein that induces angiogenesis, vascular permeability and inflammation, all of which are thought to contribute to the progression of wet AMD.

3.6 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 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. The main outcomes measured in the RCTs were 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.

Ranibizumab

4.1.2 Four RCTs of ranibizumab (MARINA, ANCHOR, PIER and FOCUS) 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 sham injection group. 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).

4.1.4 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), 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.

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 of pegaptanib compared with sham injection lost fewer than 15 letters of visual acuity from baseline to 54 weeks. Statistically significantly 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. Mean losses of 7.5 letters were 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 A 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 rather than simply treating the symptoms. 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 pegaptanib or ranibizumab. 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.

Pegaptanib

4.2.2.2 The manufacturer model for pegaptanib was a Markov state transition model comparing the cost effectiveness of the licensed dose of pegaptanib (0.3 mg) 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.

4.2.2.3 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.

4.2.2.4 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).

4.2.2.5 Results of sensitivity analysis 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 incremental cost-effectiveness ratios (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. 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.

Ranibizumab

4.2.2.6 The manufacturers 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).

4.2.2.7 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.

4.2.2.8 The modelling approach used was similar to the manufacturer's model for pegaptanib in that a Markov model 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.

4.2.2.9 The base-case ICERs over a 10-year time horizon for predominantly classic lesions were about £4,500 for ranibizumab versus PDT, and about £14,800 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.

4.2.2.10 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.

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 pegaptanib and ranibizumab 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 they are considered to be the most credible published utility values for visual loss associated with AMD.

Pegaptanib

4.2.3.4 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.

4.2.3.5 The Assessment Group carried out a sensitivity analysis 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.

4.2.3.6 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 analysis. 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.

4.2.3.7 In sensitivity analysis, 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.

4.2.3.8 In sensitivity analysis, 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 eligible cases with visual acuity of less than 6/60 receiving services), had an effect on cost effectiveness.

4.2.3.9 In terms of 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.

Ranibizumab

4.2.3.10 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.

4.2.3.11 The Assessment Group indicated that as the time horizon is reduced from the extrapolated 10 years the ICERs increase. For example, in sensitivity analysis 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.

4.2.3.12 In sensitivity analysis, 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.

4.2.3.13 In sensitivity analysis, when the injections were costed as day case rather than outpatient procedures, the ICERs increased. 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.

4.2.3.14 The cost-effectiveness estimates were most sensitive to assumptions over uptake, estimated as the proportion of eligible patients (that is, those with visual acuity 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.

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 subgroups in the ranibizumab studies, but due to differences in the trial populations, precise direct comparisons are not possible. The Committee concluded that both pegaptanib and ranibizumab have been clearly shown to

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 indicating that the beneficial effects of ranibizumab peak at 3 months after 3 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 after the third month, which is similar to that recommended in the marketing authorisation, showed ranibizumab to be less effective than in the MARINA and ANCHOR trials.

4.3.5 The Committee discussed the adverse events associated with the use of the anti-

VEGFs. The Committee heard from clinical specialists that ranibizumab and pegaptanib have a broadly similar adverse-event profile, that most adverse events are manageable and that serious ones are rare. However the Committee considered a point raised by consultees that preliminary results of an ongoing study suggests that ranibizumab may be associated with an increased risk of stroke and agreed that although this was an important issue it was inappropriate to draw conclusions at this stage.

4.3.6 The Committee considered the economic models provided by the manufacturers and the Assessment Group. It noted that the Assessment Group model incorporated additional costs of drug administration and monitoring, which the clinical specialists felt had been underestimated in the manufacturers' models. The Committee thought that the Assessment Group model considered more fully and appropriately the

extrapolation into the future of costs and benefits associated with these treatments, and did so for both drugs in a comparable way. The Committee concluded that the Assessment Group model provided more plausible results and more fully explored the uncertainty in assumptions.

4.3.7 The Committee discussed key parameters which were fundamental to determining the cost effectiveness of the treatments. These were the:

- possible benefits associated with anti-VEGF treatment beyond the 2 years reported in the clinical trials
- possible costs associated with anti-VEGF treatment beyond 2 years
- difference between the costs and benefits associated with the licensed regimen of ranibizumab and the regimen used in the MARINA and ANCHOR RCTs

- costs of adequate facilities and staffing for intravitreal injection
- utilities used in the modelling
- costs related to blindness, including low-vision aids, visual rehabilitation and community care
- cost effectiveness of ranibizumab and pegaptanib for subgroups of CNV.
- relative benefits of the treatment of the better-seeing and the poorer-seeing eye.

4.3.8 The Committee was concerned 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 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, though 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 although this was not known, the assumption could be accepted as the basis for decision making.

4.3.9 The Committee was concerned about the models' assumptions that costs of treatment stopped after 2 years and that this had a considerable effect on the ICERs generated. It understood that CNV may recur after cessation of treatment. 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 in the future which are not included in the economic models.

4.3.10 The Committee was also concerned about the modelling of costs related to differences in the licensed regimen of ranibizumab compared with that used in the MARINA and ANCHOR RCTs, which were used to model clinical effectiveness. The Committee was mindful of the results of the PIER study showing that the reduced frequency regimen was associated with reduced benefits. Nevertheless it heard from clinical specialists that the licensed dose is the one most likely to be used in practice and that the costs of treatment in the first 2 years in the Assessment Group model could be considered high. Taking this into account and the concerns expressed in section 4.3.9 about the costs of treatment beyond 2 years, the Committee concluded that on balance it would be reasonable to accept a base-case scenario in which total cost was based on 24 doses.

4.3.11 The Committee discussed the assumptions in the models for the cost 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 heard from the Assessment Group that the sensitivity analysis in its economic model in which intravitreal injections were assumed to be given as a day case procedure was broadly in line with costs anticipated by the clinical specialists. Thus the Committee concluded that the sensitivity analysis using costs for day case treatment from the Assessment Group were the closest estimates of the actual costs incurred in practice by the NHS.

4.3.12 The Committee discussed the utilities used in the models. It considered that it may 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 manufacturers' models. It noted that use of the EQ-5D might result in a much smaller difference, perhaps by as much as a factor of 4, between utilities reflecting the best and worst vision states in the economic models, but nevertheless accepted the utilities used in the Assessment Group model as a guide to its decision making.

4.3.13 The Committee heard from the clinical specialists that assumptions in the Assessment Group model for costs related to blindness (such as registration, low-vision aids, and rehabilitation) were low, if not for standard practice, then for best practice. This would mean that the incremental costs associated with anti-VEGFs compared with standard treatment had been overestimated because use of anti-VEGFs would save more on costs related to blindness.

However, the Committee concluded that on balance, overestimation of the QALY gain discussed in 4.3.12 could be offset by this overestimation of the incremental costs, and therefore accepted both the utility and cost of blindness assumptions in the Assessment Group model.

4.3.14 The Committee discussed the variation in cost effectiveness of ranibizumab by lesion subgroup. In view of its considerations regarding the assumptions used for economic evaluation, the Committee considered that the most plausible ICER for ranibizumab compared with best supportive care in patients with minimally classic or occult no classic CNV was £35,200 per QALY gained. For ranibizumab compared with best supportive care in patients with predominantly classic lesions the most plausible ICER was £17,800 per QALY gained. For ranibizumab compared with PDT in patients with predominantly classic lesions

the most plausible ICER was £26,100 per QALY gained. It concluded that the use of ranibizumab could be considered cost effective in predominantly classic lesions (consistent with the population in the trials), but not in minimally classic or occult no classic lesions.

4.3.15 The Committee considered the cost effectiveness of pegaptanib in view of its considerations regarding the assumptions used for economic evaluation. It noted that although pegaptanib was less expensive than ranibizumab, it was also notably less clinically effective. It considered the most plausible ICER for pegaptanib compared with best supportive care to be £47,800 per QALY gained. It discussed whether there was clear evidence of cost effectiveness of pegaptanib in any particular subgroup and considered that this was not the case. It concluded that pegaptanib is not cost effective for the treatment of wet AMD.

4.3.16 The Committee discussed the cost effectiveness of treating only the better-seeing eye compared with treating the worse-seeing eye. The Committee noted that both the manufacturers' models and the Assessment Group model reflected the cost effectiveness of treating the better-seeing eye only and that no cost effectiveness estimates were presented for the treatment of both eyes. It understood that the reduction in quality of life of moving from binocular vision to monocular vision was much smaller than the reduction in quality of life from moving from monocular vision to very poor vision. It was therefore of the opinion that the cost effectiveness of anti-VEGFs would be markedly poorer if calculations had been based on the treatment of the worse-seeing eye. The Committee concluded that ranibizumab is only cost effective compared with standard treatment if treatment is for the better-seeing eye only.

4.3.17 The Committee considered combination use of ranibizumab and PDT. It noted that the FOCUS trial showed improved visual acuity when patients were treated with ranibizumab plus PDT compared with PDT alone. However the results for combination therapy were no better than the results for monotherapy seen in the other trials. The evidence presented for this appraisal did not include any estimates of the cost effectiveness of combination therapy compared with standard practice. It noted that the marketing authorisation for ranibizumab does not specify whether its recommendations apply to combination therapy or monotherapy alone. The Committee concluded that it was not in a position to make recommendations about combination use.

4.3.18 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 further concluded that treatment with ranibizumab is cost effective compared with standard care for patients with predominantly classic CNV but not for use in patients with minimally classic or occult no classic AMD, and that treatment with pegaptanib is not cost effective for the treatment of wet AMD.

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
- about the cost effectiveness of ranibizumab in combination with PDT compared with PDT alone.

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 April

2010. The Institute would particularly welcome comment on this proposed date.

Andrew Stevens

Chair, Appraisal Committee

April 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

Chief Executive, Women’s Nationwide Cancer Control Campaign

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

Clinical Senior Lecturer, The University of Manchester

Mrs Eleanor Grey

Lay representative

Dr Catherine Jackson

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

Dr Peter Jackson

Clinical Pharmacologist, the University of Sheffield

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 make submissions and comment on the draft scope and assessment report. They are also invited to comment on the Appraisal Consultation Document (ACD). Consultee organisations 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