NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

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

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the Assessment Report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

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. Deteriorating vision is associated with loss of independence and an increased risk of falls, fractures and depression.

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 photoreceptor cells in the

centre of the retina (a process known as choroidal neovascularisation). These vessels easily haemorrhage and cause lesions on the macula, leading to visual impairment. Dry AMD (non-neovascular) is a form of extensive atrophy (wasting) of cells which progresses slowly, whilst the wet form leads to a rapid worsening of vision.

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. The most cited risk factor for AMD is cigarette smoking, with research showing that former smokers have a 3.6 times greater risk of AMD compared to people who have never smoked.

Choroidal neovascularisation (CNV) is classified according to its appearance on fluorescein angiography (a technique used to examine blood vessels in the retina). The classifications are:

- classic with no occult (classic CNV lesions with no evidence of an occult component)
- predominantly classic with occult (classic CNV forms at least 50% of the lesion but some occult CNV is present)
- minimally classic (classic CNV makes up less than 50% but more than 0% of the lesion)
- occult only (no classic CNV seen).

Further subdivisions can be made based on where the lesions occur relative to the fovea (the central part of the macula with the area of highest visual acuity). Subfoveal lesions are located behind the middle of the fovea. This is the most common site. Juxtafoveal lesions are located within 200 micrometres of the fovea but not in the middle, and extrafoveal lesions are located more than 200 micrometres outside the fovea.

The evidence-base for this appraisal consists of patients with subfoveal wet AMD with various types of CNV lesions.

1.2 Current management

Treatments for AMD are very limited. For most patients management is limited to social support, visual rehabilitation and the provision of aids to help with low vision. However, in those with classic no occult subfoveal CNV and a best corrected visual acuity of 6/60 or better, photodynamic therapy (PDT) is an option. (Visual acuity of 6/60 means that the patient can see at 6 metres what someone with normal vision, that is 6/6, could see from 60 metres away). Current NICE guidance recommends PDT for patients with classic no occult lesions; its use in predominantly classic lesions is not recommended except in clinical trials. PDT involves injecting verteporfin, a photosensitive drug that remains in the new blood vessels in the eye. Treatment with a low powered laser 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.

2 The technologies

Ranibizumab and pegaptanib both inhibit the activity of vascular endothelial growth factor (VEGF) and are commonly known as anti-VEGFs. Ranibizumab is a humanized therapeutic antibody fragment that binds to VEGF-A isoforms. Pegaptanib is a pegylated modified oligonucleotide that binds to VEGF-165. Both drugs reduce new vessel growth and leakage.

Both drugs hold UK marketing authorisations for the treatment of neovascular (wet) age-related macular degeneration and are administered by intravitreal injection into the affected eye. Pegaptanib should be administered once every six weeks (nine injections per year). Ranibizumab treatment is initiated with a loading phase of one injection per month for three consecutive months, followed by a maintenance phase in which patients should be monitored for visual acuity on a monthly basis. If the patient experiences a loss of more than 5 letters in visual acuity (ETDRS or one Snellen line equivalent), ranibizumab

should be administered. A ETDRS or Snellen chart consists of seven rows of letters which get smaller down the chart. The interval between two doses should not be shorter than one month.

Anti-VEGFs are associated with adverse events which may be related to the intravitreal injection or to the drugs themselves. The adverse events may be eye-related (ocular) or systemic, and can include vitreous floaters, conjunctival haemorrhage, eye pain, increased intraocular pressure, intra-ocular inflammation, ocular or periocular infections, endophthalmitis (severe infection inside the eye), hypersensitivity reactions, and retinal detachment.

Table 1: Summary description of the technologies

Generic name	ranibizumab	pegaptanib
Proprietary name	Lucentis	Macugen
Manufacturer	Novartis Pharmaceuticals Ltd	Pfizer Ltd
Dose	0.5 mg	0.3 mg
Acquisition cost excluding VAT (BNF edition 53)	£761.20 per injection (not yet in BNF, NICE notified of price by manufacturer)	£514. 00 per injection

3 The evidence

3.1 Clinical effectiveness

The Assessment Group's systematic review identified two randomised controlled trials (RCTs) of pegaptanib and two published RCTs of ranibizumab. In addition, Novartis submitted reports of two additional RCTs which were unpublished at the time the Assessment Report was written. The Assessment Group considered all of these to be of high quality. For further details of the studies see table 3.1 on page 51 of the Assessment Report.

Pegaptanib

The combined results of two concurrent RCTs comparing doses of 0.3, 1.0 and 3.0 mg pegaptanib with sham injection (one carried out in the USA and Canada, the other at centres worldwide) 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.

Ranibizumab

Four RCTs of ranibizumab (MARINA, ANCHOR, PIER, FOCUS) were included in the Assessment Report and manufacturer's submission. For details of the interventions, comparators and CNV lesion types in the four RCTs, please refer to table 5 of this overview. 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. Outcomes were assessed at different time points and trials had a different number and frequency of injections given to the intervention group.

3.1.1 Assessment of effectiveness outcomes

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
- adverse events.

3.1.1.1 Loss in visual acuity

The primary outcome measure was a loss of less than 15 letters on the EDTRS or Snellen charts between baseline and follow-up time points. The Assessment Group remarked that the loss of more than 15 letters (3 lines on

the EDTRS chart) is a clinically meaningful change in visual acuity as it can determine the difference between being able to live independently, drive, read and watch television, or being dependent.

Statistically significantly more patients receiving 0.3 mg of pegaptanib compared with sham injection lost less than 15 letters of visual acuity from baseline to 54 weeks. Statistically significantly more patients receiving 0.5 mg ranibizumab compared with both sham injection (MARINA study), and PDT (ANCHOR study), lost less than 15 letters of visual acuity from baseline to 12 months. See table 2 below and page 59 of the Assessment Report for more details.

Table 2: Summary results of the proportion of patients losing less than 15 letters

Outcomes	**No of patients (%) gaining or losing letters**	
VISION TRIAL YEAR 1 (All types of lesions)	**0.3mg pegaptanib (n=294)**	**sham injection (n=296)**
Loss of <15 letters at week 54 p value vs sham	206 (70) p<0.001	164 (55)
VISION study year 2 (Patients re-randomised)	**0.3mg – discontinue (n=132)**	**sham – any dose (n=165)**
Loss of <15 letters Week 54	76%	56%
MARINA Lesion type: occult/MC	**0.5mg ranibizumab (n=240)**	**sham (n=238)**
Loss of <15 letters 12 months (primary outcome) p value (vs sham) 24 months p value (vs sham)	227 (94.6) p<0.0001 216 (90.0) p<0.0001	148 (62.2) 126 (52.9)
ANCHOR Lesion type: PC	**0.5mg ranibizumab + sham PDT (n=139*)**	**sham injection + PDT (n=143)**
Loss of <15 letters	134 (96.4)	92 (64.3)
PIER Lesion type: mixed	**0.5mg ranibizumab (n=61)**	**sham (n=63)**
Loss of <15 letters p value (vs sham)	55 (90.2) p<0.0001	31 (49.2)
FOCUS Lesion type: PC/MC	**0.5mg ranibizumab + PDT (n=105)**	**sham + PDT (n=56)**
Loss of <15 letters p-value (vs sham)	95 (90.5) p=0.0003	38 (67.9)

PC; predominantly classic, MC; minimally classic, PDT; photodynamic therapy
* one patient excluded due to missing baseline VA score.

3.1.1.2 Maintenance or gain in visual acuity

Patients treated with both pegaptanib and ranibizumab gained in visual acuity. The proportion gaining 15 or more letters was higher for ranibizumab than for pegaptanib.

In the VISION study (pegaptanib), statistically significantly more patients in the 0.3 mg group gained at least five letters (22%) compared with 12% for the sham group (p = 0.004). Gains of at least 10 letters were also reported for 11% of the 0.3 mg pegaptanib group (p=0.02) compared to 6% of the sham injection group. Very few patients gained more than 15 letters.

A third of the 0.5 mg ranibizumab group gained at least 15 letters compared to 4% of the sham group at 24 months in the MARINA RCT. In the ANCHOR trial, 40% of the 0.5mg ranibizumab group gained at least 15 letters compared to 6% of the PDT sham injection group. In the FOCUS study, 24% of the 0.5mg ranibizumab + PDT group compared to 5% of the sham injection + PDT group gained at least 15 letters (p=0.0033).

3.1.1.3 Mean change in visual acuity

Pegaptanib

Mean loss of letters at week 54 was higher in the sham group than in the 0.3 mg group. 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.

Ranibizumab

The MARINA, ANCHOR and FOCUS trials all reported mean increases in visual acuity in the 0.5 mg ranibizumab group compared to the sham injection group. 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). Corresponding losses in the sham groups were 8.2 letters in the FOCUS trial and 10.5 letters in the MARINA trial and these differences were statistically significant. PIER trial patients experienced a decrease in visual acuity and this may have been because doses were administered every three months instead of monthly as in the other trials. For

more details on mean changes in visual acuity see table 3.4 on page 63 of the Assessment Report.

3.1.1.4 Deterioration to legal blindness

Legal blindness was defined in the studies as the Snellen equivalent of 20/200 (6/60) or worse.

Pegaptanib

By the end of the first year VISION study 56% of patients in the sham group were legally blind in the study eye compared to 38% in the 0.3 mg pegaptanib group. After re-randomisation at week 54, only one extra patient who continued the 0.3 mg dose had deteriorated to legal blindness compared to 14% who discontinued the 0.3 mg dose after one year. In the second year of the VISION study, approximately 34% of those randomised to continue with 0.3mg pegaptanib were legally blind compared with 24% of those randomised to discontinue 0.3mg pegaptanib and 47% of those in the control arm.

Ranibizumab

In the PIER study, [redacted] of patients in the ranibizumab group deteriorated to legal blindness compared to over [redacted] in the sham group. A total of 15% of patients in the MARINA trial reached the level of legal blindness in the 0.5mg ranibizumab group compared with 48% in the sham group at 24 months. In the ANCHOR trial, 60% of patients receiving sham injection deteriorated to legal blindness compared with 16% receiving 0.5 mg ranibizumab and PDT at 24 months. Please refer to table 3.5 on page 65 of the Assessment Report for more details.

3.1.1.5 Anatomical changes from baseline

Pegaptanib

The VISION study reported a slower rate of increase in CNV lesions between baseline and week 54 for the 0.3 mg compared with the sham group (1.8 disc areas for 0.3mg group vs 2.5 disc areas for the sham group). Of those who continued with pegaptanib after 54 weeks, mean lesion size was 5.4 disc

areas (DA) at week 78 and 5.6 DA at week 102 in the 0.3 mg group, compared with 7.5 DA and 8.1 DA in the group who discontinued ($p<0.05$).

Ranibizumab

People in the MARINA trial treated with 0.5mg ranibizumab showed no change in area of CNV between baseline and the end of two years of treatment. By contrast, people in this study who received sham injection experienced an average increase in CNV area of 2.58 disc areas over two years. Patients in the ANCHOR and FOCUS trials who received 0.5mg ranibizumab experienced a decrease in CNV area compared to the sham groups. However, patients who received fewer injections in the PIER trial experienced an increase in CNV lesions, although the increase was lower than in the sham group. This may indicate that the number and frequency of injections is a critical factor in the effectiveness of ranibizumab.

3.1.1.6 Change in visual function questionnaire scores (NEI VFQ-25)

This outcome was reported for ranibizumab only. In the MARINA (ranibizumab) trial there was an [redacted] of nearly [redacted] points in the mean near activities score for ranibizumab patients compared with a mean [redacted] of [redacted] points in the sham group**.** Both ranibizumab groups showed an [redacted] of about [redacted] points in distant activities score compared with a mean [redacted] of [redacted] points for the sham group. The ANCHOR trial found [redacted] in near activities score. All treatment groups showed an [redacted] in the distant activities score but mean scores were [redacted] for the ranibizumab treatment group than for the PDT group. The PIER study showed [redacted] between treatment and sham groups which may have been a result of the reduced dose frequency in this study.

3.1.1.7 Disease modifying effect

This outcome was reported for pegaptanib only. A study reported that the risk of non-response at the end of two years was lower for people who discontinued pegaptanib after a year compared to those who had never

received the drug. The Assessment Group considered this to be evidence of a disease modifying effect, which is biologically plausible because anti-VEGF drugs target the underlying disease rather than just treat the symptoms of AMD. However, it also noted that the decline in the proportion of responders (those losing less than 15 letters) from 54 weeks to 102 weeks in the VISION study was the same for those who received the 0.3 mg dose and those who had never received the drug (14%).

3.1.1.8 Adverse Events

Pegaptanib

In the VISION study most adverse events reported were mild to moderate events. They were similar between treatment arms except for vitreous floaters, vitreous opacities, and anterior chamber inflammation after one year of treatment. Eye related adverse events were more common in the study eye among patients in the sham injection group suggesting that the preparation procedure itself (which included an ocular antisepsis procedure and an injection of subconjunctival anaesthetic) may be associated with adverse effects. Endophthalmitis affected about 1.3% of the patients in the first year. Of these, two thirds had been affected by protocol violation (for example, failure to use aseptic technique).

Ranibizumab

In the ranibizumab studies, most adverse events were also mild to moderate. Conjunctival haemorrhage was the most widely reported eye related adverse effect, but incidence varied between the ranibizumab RCTs and it was also high in the control groups. More ranibizumab patients than control patients experienced increased intraocular pressure and vitreous floaters. Endophthalmitis affected approximately 1% and 0.7% of patients in the MARINA and ANCHOR RCTs respectively. In the FOCUS trial, intraocular inflammation was [redacted] in the ranibizumab + PDT group compared to [redacted] in the PDT + sham group.

3.1.1.9 Subgroup analysis

Main outcomes examined were mean decrease in visual acuity by lesion type and CNV status. Consultees indicated that consideration of subgroups by CNV lesion type and baseline visual acuity may be important to consider. More details on subgroup analysis can be found on page 66–68 of the Assessment Report.

3.2 Cost effectiveness

3.2.1 Published literature

The Assessment Group identified a total of 421 publications relating to cost-effectiveness in AMD. None of these were a fully published economic evaluation 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. The detailed results of this review are presented in section 4.1.1 of the Assessment Report, pages 88–92.

3.2.2 Manufacturer submissions

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 two 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.

3.2.2.1 The Pfizer model - pegaptanib

The Assessment Group reported that the Pfizer model is a Markov state transition model comparing the cost effectiveness of the licensed dose of pegaptanib (0.3 mg) every six weeks for a maximum of two 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.

The model has 12 states, defined by declining visual acuity from 6/12 through 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 where a person cannot drive. The base-case analysis is based on all lesion types. 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 and the cost-effectiveness of treatment adopting an alternative stopping rule, labelled scenario B, with a higher threshold visual acuity (6/60) for discontinuing pegaptanib treatment, is also reported in the submission.

Cycle length in the model is six weeks, and there is a ten year horizon (life expectancy of patients with a mean age of 77). The Assessment Group indicated that no adjustments were made to quality of life scores for patients experiencing adverse events and no adverse events were reported for the usual care cohort even though they were expected for PDT. The analysis was based on the treatment of the patients' better-seeing eye only and the Assessment Group commented that the incremental cost-effectiveness ratios (ICERs) for the treatment of the worst eye or both may be higher. See table 3 below for the base case results of these two scenarios.

Table 3: Base-case results from the Pfizer model

Scenario type	Pegaptanib costs	Usual care costs	Pegaptanib QALYs	Usual care QALYs	Incremental costs per patient	Incremental QALY per patient	ICER
Scenario A	£20,763	£16,058	3.333	3.035	£4,705	0.298	£15,815
Scenario B	£19,515	£15,406	3.386	3.097	£4,109	0.289	£14,202

The Assessment Group commented that the cycle length of about six weeks was based on the VISION trial rather than its appropriateness to the rate of disease progression in either cohort in the model. The Assessment Group also noted that patients in the Pfizer model had a single fluorescein angiogram prior to treatment and no further imaging, and that this is in sharp contrast to current clinical practice. Clinical experts indicated that patients would also have optical coherence tomography (OCT) and repeat fluorescein angiography every three or six months.

Results for 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 ICERs. For example, the ICER for a three year time horizon was between £55,000 and £60,000 per QALY, reducing to £30,000 per QALY when the time horizon was increased to five years. The Assessment Group argues that this reflects the fact that treatment costs are incurred in the first two years with benefits being projected over the patient's lifetime. Similarly when costs and probabilities of receiving services for visual impairment are set at the upper limits, then pegaptanib treatment dominates usual care, whereas if they are set to the lower limit the ICER is around £25,300 per QALY for scenario A and about £24,200 per QALY for scenario B. When age was considered in the sensitivity analysis, the ICER was reduced to about £10,900 for base-case (about £9,500 for scenario B) for patients under 75 years and about £18,900 for base-case (£17,100 for scenario B) for patients above 75 years.

Sensitivity analysis by the Assessment Group using the Pfizer model

The Assessment Group tested the sensitivity of cost effectiveness estimates to changes in assumptions on resource use for patient monitoring. The cumulative effect of the changes is to increase the ICER from about £15,800 per QALY gained in the base-case to about £22,300 per QALY gained. When the injection procedure is costed as a day case procedure, the ICER increases to about £35,200. Please refer to table 4.

Table 4: Summary of sensitivity analyses using the Pfizer model

	Incremental cost	Incremental QALYs	ICER
OCT cost at each attendance	£5,356	0.298	£17,974
Vision assessment cost at each attendance	£6,099	0.298	£20,467
Fluorescein angiography every six months	£635	0.298	£22,266
Cost injection as day case procedure	£10,489	0.298	£35,197
Costs as in submission. Utilities from Novartis submission	£4,705	0.279	£16,863

3.2.2.2 Novartis model

The Assessment Group noted that the Novartis 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 for predominantly classic, MARINA for minimally classic and occult no classic, PIER for all lesion types). Please refer to table 5 for more details on the trials. Because the ANCHOR trial did not include a sham arm, the Assessment Group noted that comparison of treatment with ranibizumab against best supportive care for predominantly classic patients was made through indirect comparison using data from the TAP study in which PDT was compared with best supportive care. MARINA trial data was also used to estimate the natural history of the disease for extrapolating trial outcomes over ten years.

The modelling approach used was similar to the Pfizer approach where 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 two years and 12 injections over a year respectively, but in the base-case analysis for the model, eight injections in year 1 and six injections in year 2 (as per the marketing authorisation) were used with the assumption that the same clinical efficacy would be achieved with this lower dosing frequency.

Utilities used in the economic model were derived from a study sponsored by the manufacturer to derive appropriate health state valuations from a general population.

The Assessment Group also noted that resource use assumptions for PDT in the model included an estimate that 7.5% of patients will receive intravitreal injection of triamcinolone. No evidence of this could be found in clinical trials or supporting documents in the submission. The model included the costs of administering injections in the sham arm of the trials and the Assessment Group believed that this was inappropriate since it did not reflect clinical practice. In addition the impact of adverse events was not taken into account in the submission, and neither was the cost of managing these events. There was a double counting error which caused the comparator to be more costly by £51–£141 in each treatment cycle, thereby underestimating the cost difference between PDT and ranibizumab.

Table 5: Base-case results from Novartis model

Trial	Lesion type	Intervention	Comparator	ICER
ANCHOR	Predominantly classic	ranibizumab 0.5 mg	PDT	£4,489
ANCHOR	Predominantly classic	ranibizumab 0.5 mg	Indirect comparison with BSC	£14,781
PIER	All types of AMD lesions	ranibizumab 0.5 mg	BSC	£12,050
MARINA	Occult no classic lesions	ranibizumab 0.5 mg	BSC	£26,454
MARINA	Minimally classic lesions	ranibizumab 0.5 mg	BSC	£25,796

PDT; photodynamic therapy BSC; best supportive care AMD; age-related macular degeneration

Similar results to the base-case analyses are reported for the probabilistic sensitivity analyses. The manufacturer's submission states that the probability of ranibizumab being cost effective at a willingness to pay (WTP) 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, 59% for minimally classic, and 57% for occult no classic for a WTP threshold of £30,000 per QALY. The Assessment Group noted that the results reported here are based on the assumption that frequency of dosage of ranibizumab can be reduced, from twelve to eight injections (the latter including a loading dose of monthly injections for the first three months) in year 1 and from twelve to six injections in year 2, without reducing its effectiveness.

Sensitivity analysis by the Assessment Group using the Novartis model

The Assessment Group carried out sensitivity analysis on some of the key parameters in the manufacturer's model, listed in table 6 below. The analysis was based on different lesion types and the comparators used are given in brackets. After removing the double counting error and the costs of administering sham injections for all comparisons, the ICERs did not change significantly (ICERs increased by between £1,000 and £4000 per QALY for all the scenarios, see first and second rows of table 6). However the main driver of ICERs seems to be the number of ranibizumab injections. For example, in the predominantly classic lesions group the ICERs for all the scenarios were

below £30,000, except in the case where the number of ranibizumab injections given in the ANCHOR trial was used. When the number of injections given in the MARINA trial is used the ICERs are about £56,200 per QALY compared to the initial figure of about £30,700 per QALY when fewer injections are used.

Table 6: Summary of sensitivity analyses using the Novartis model

Model changes	Lesion type and the ICERS			
	PC (PDT)	PC (BSC)	MC (BSC)	OC (BSC)
As reported in submission (8 injections in first year, 6 in second year)	£ 4,489	£ 14,781	£ 25,796	£ 26,454
After adjusting costs for errors	£ 8,121	£ 15,322	£ 27,174	£ 27,767
9 injections in first year	£ 13,135	£ 19,042	-	-
12 injections in first year (as in ANCHOR trial)	£ 28,176	£ 30,203	-	-
9 in first year; 6 in second year	-	-	£ 30,227	£ 30,777
12 in first year; 12 in second year (as in MARINA trial)	-	-	£ 55,906	£ 56,234

PC; predominantly classic, MC; minimally classic, OC; occult only, PDT; photodynamic therapy, BSC; best supportive care

3.2.3 Assessment group model

The Assessment Group's model was based on the cost effectiveness of ranibizumab and pegaptanib compared with current practice (PDT with verteporfin for classic no occult lesions or predominantly classic lesions if the evidence-base is limited and best supportive care). They used the following clinically accepted categories of response; intermediate vision loss (loss of 15 to 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.

A six state Markov model was developed and the rate of disease progression was expressed as the reduced probability of progressing to a lower level of visual acuity health state in each model cycle. The model extrapolated the effects of the two 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.

The Assessment Group also assumed that patients only benefit while on treatment with both drugs and that all patients experience a rapid worsening of their condition as soon as treatment stops, reverting to the state of visual deterioration they would have reached had they received no treatment. 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.

3.2.3.1 Cost effectiveness of pegaptanib in Assessment Group model

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

Sensitivity analysis in the Assessment Group model for pegaptanib

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 two 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.

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 discontinue treatment after one 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 greater

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 three of the ten year model.

Varying the distribution of initial visual acuity has a significant effect on the ICER. A cohort equally split between the 6/12 and 6/24 and 6/24 and 6/60 states produced an ICER of approximately £35,900, while a cohort with initial visual acuity of 6/24–6/60 produced an ICER of approximately £46,300.

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

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

Table 7 reports the assumptions described above which had a substantial impact on the ICERs.

Table 7: Deterministic sensitivity analysis for pegaptanib (Assessment Group model)

		ICER
Reference case	**10 years**	**£ 30,986**
Time horizon	5 years	£ 49,076
	3 years	£ 87,428
Disease modifying effect	Year 3 onwards	£ 20,467
Visual acuity at baseline (6/12–6/24)	50% 6/12–6/24 and 50% 6/24–6/60	£ 35,913
	6/24–6/60	£ 46,285
Number of injections	9 in Year 1 (8.4)	£ 32,752
	9 in Year 1 (8.4) and 8 in Year 2 (6.9)	£ 35,676
Cost of injection procedure	Costed as day case procedure	£ 47,845
Costs of blindness	Low uptake/ low costs	£ 40,582
	High uptake/ medium costs	£ 14,230

3.2.3.2 Cost effectiveness of ranibizumab in Assessment Group model

In trial-based case analysis, ranibizumab was compared to best supportive care and PDT for different lesion types; predominantly classic, minimally classic and occult no classic. In table 8 below, the base case ICERs at ten years for the different lesion types are reported.

Table 8: Base case ICERs for ranibizumab (Assessment Group model)

Lesion type	Base case	ICERS
Predominantly classic: ANCHOR trial. PDT as comparator	10 years	£15,638
Predominantly classic: ANCHOR trial. Best supportive care as comparator	10 years	£11,412
Minimally classic and occult no classic: MARINA trial. Best supportive care as comparator	10 years	£25,098

The costs of blindness are between 24% and 54% of total costs for ranibizumab patients. While the difference between cost of blindness in the ranibizumab and comparator cohorts at ten years does not fully offset the costs of treatment with ranibizumab, the increased proportion of total costs accounted for by progression to greater visual impairment and blindness, together with the increased QALY gain, yields the lower ICERs reported in table 8 above.

Sensitivity analysis in the Assessment Group model for ranibizumab

The results of the sensitivity analysis reported here are those with a strong effect on cost effectiveness estimates. The full sensitivity analysis can be found in the Assessment Report on pages 145–147.

As the time horizon is reduced from the extrapolated 10 years the ICERs increase (see table 9 below).This is because the incremental cost of ranibizumab reduces whilst the incremental QALY gain increases. The number of injections also influences the ICERs considerably. For patients with predominantly classic lesions, with an assumed maximum treatment duration of one year (as observed in the ANCHOR trial), reducing the number of injections from 12 to 9 reduces the ICER from approximately £15,600 to about

£6,900 (56% reduction) for the comparison with PDT and from £11,400 to about £6,100 (47% reduction) for the comparison with best supportive care.

For patients with minimally classic and occult no classic lesions, with an assumed maximum treatment duration of two 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.

When the injections were costed as day case procedures, the ICERs generally increased. In particular for patients with predominantly classic lesions receiving a maximum of one 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 approximately £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 approximately £35,200.

The results also showed that the cost effectiveness estimates were most sensitive to assumptions over uptake, estimated as the proportion of eligible cases (that is, with visual acuity less than 6/60) receiving services. Using high uptake and high unit cost estimates produces a situation where ranibizumab is dominant (lower cost with 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 ICERs generally increase from baseline. Please refer to table 9.

Table 9: Sensitivity analysis for ranibizumab (Assessment Group model) Source: Assessment Report pages 145–147.

	RMB vs PDT (PC Lesions)	RMB vs BSC (PC Lesions)	RMB vs BSC (MC or occult no classic)
	ICER	ICER	ICER
Reference case (10 years)	**£ 15,638**	**£ 11,412**	**£ 25,098**
5 years	£ 21,801	£ 15,862	£ 43,441
3 years	£ 35,744	£ 26,774	£ 80,105
Number of injections			
9 in Year 1 (12)	£ 6,897	£ 6,087	n/a
9 in year 1 (12) and 6 in year 2 (12)	n/a	n/a	£ 12,649
Cost of injection procedure (costed as day case procedure)	£ 26,102	£ 17,787	£ 35,157
Costs of blindness			
High uptake/ high costs	RMB dominates	RMB dominates	£ 2,583
Low costs/ medium uptake	£ 19,967	£ 16,281	£ 29,446

RNB; ranibizumab, BSC; best supportive care, PC; predominantly classic, MC; minimally classic

3.2.4 Summary base-case results for both drugs (Assessment Group model, 10 year time horizon)

Tables 10 and 11 below summarise the base-case results for both drugs and the probability of the drugs being cost effective at a WTP threshold of £20,000 and £30,000 per QALY.

Table 10: Summary base case results (10 years)

Lesion type	Pegaptanib		Ranibizumab	
	Manufacturer	Assessment Group	Manufacturer	Assessment Group
All lesion type (vs BSC)	£15,815	£30,986	£12,050	n/a
Predominantly classic (vs PDT)	n/a	n/a	£4,489	£15,638
Predominantly classic (vs BSC)	n/a	n/a	£14,781*	£11,412
Minimally classic /occult no classic (vs BSC)	n/a	n/a	£25,796/£26,454	£25,098

* Based on indirect comparison with best supportive care (BSC)
PDT; photodynamic therapy

Table 11: Summary of willingness to pay thresholds for ranibizumab and pegaptanib

	Probability of being cost effective			
WTP threshold	**Pegaptanib**	**Ranibizumab**		
	All lesion types vs BSC	PC lesions vs PDT	PC lesions vs BSC	MC/OC vs BSC
£20,000	17%	72%	95%	15%
£30,000	58%	97%	99%	81%

BSC; best supportive care, PDT; photodynamic therapy, PC; predominantly classic, MC/OC; minimally classic, occult no classic

4 Issues for consideration

- Ranibizumab is used in a different dose frequency regimen (lower frequency of injections) in the pivotal RCTs to that recommended in the marketing authorisation. How does this impact on considerations of its clinical and cost effectiveness?
- Current NICE guidance recommends PDT for patients with classic with no occult lesions, and not in those with predominantly classic lesions except in clinical trials. What is current practice in England and Wales and how does this impact on the cost-effectiveness evidence for anti-VEGF drugs compared with PDT?
- The analyses are based on treating the eye with better vision only. How might this affect considerations of the cost effectiveness of pegaptanib?
- There are no head-to-head trials comparing ranibizumab with pegaptanib. No indirect comparisons have been performed due to differences in RCT populations.
- Possible subgroups might be defined by CNV lesion type or by baseline visual acuity. Is there any evidence to suggest that clinical or cost effectiveness for any such group differs from others?
- Consultees state that recurrent CNV on cessation of treatment is highly likely. What are the considerations of how disease progression after ceasing treatment has been modelled?
- Costs: Do the costs of monitoring, administration, and rehabilitation in the models reflect clinical practice and are the assumptions for projecting them over 10 years reasonable? For example, how often are

monitoring investigations such as fluorescein angiography and OCT needed? How are the costs of rehabilitation expected to increase over time due to deterioration of an individual's condition, technological improvements and inflation?

5 Ongoing research

There are currently a number of phase II and III trials of anti-VEGF treatments for AMD which are ongoing or about to start. These include:

- Protocol EOP1009 – A phase II trial to assess the effect of pegaptanib sodium on foveal thickening in patients with exudative subfoveal AMD.
- A phase IIIb/IV trial to compare the safety and efficacy of intravitreal injections of pegaptanib. Expected completion: October 2008. NCT00134667.
- An exploratory randomized trial to explore the safety and efficacy of three different doses of intravitreous injections of pegaptanib in patients with subfoveal neovascular (AMD). Expected completion: June 2009. NCT00312351.
- HORIZON: a phase III trial in patients with subfoveal CNV secondary to AMD. Sham injection control. Objectives: to investigate long-term safety, tolerability and efficacy of multiple intravitreal ranibizumab. Completion date not given.
- SAILOR: phase IIIb single-masked, 1 year multicentre study (NCT00299078). The primary outcome is the incidence of serious adverse events in ranibizumab treated patients. Study start: March 2006. Completion date not given.
- Verteporfin photodynamic therapy cohort study for the UK. This is a study aimed at describing the provision and outcomes of PDT in NHS setting. Relationship between QoL/resource use and VA can be extrapolated to existing RCT findings from this study. Expected completion date: 31 December 2007

6 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The Assessment Report: Colquitt JL, Jones J, Tan SC, et al. (August 2006). Southampton Health Technology Assessments Centre, University of Southampton. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

B Submissions from the following organisations:

I Manufacturers/sponsors:

- Pfizer
- Novartis Pharmaceuticals

II Professional/specialist and patient/carer groups:

- Royal National Institute of the Blind (RNIB)
- Macular Disease Society (MDS)
- Royal College of Nursing
- Royal College of Ophthalmologists

III Commentator organisations (without the right of appeal):

- None

C Additional references used:

- Guidance on the use of photodynamic therapy for age-related macular degeneration (2003). Available from:www.nice.org.uk/TA068
- EMEA scientific discussions for pegaptanib (2006) and ranibizumab (2007)