

Ranibizumab for treating diabetic macular oedema

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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This guidance replaces TA237.

1 Guidance

- 1.1 Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:
- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
 - the manufacturers of ranibizumab (branded or biosimilar) provide it at a discount level no lower than the discount agreed in the patient access scheme.
- 1.2 People currently receiving ranibizumab for treating visual impairment due to diabetic macular oedema whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

- 2.1 Ranibizumab (Lucentis, Novartis) belongs to a class of drugs that blocks the action of vascular endothelial growth factor A (VEGF-A). In diabetic macular oedema, VEGF-A causes blood vessels to leak in the macula, the area of the retina responsible for the clearest vision. The accumulated fluid causes swelling, or oedema, which impairs vision. By inhibiting the action of VEGF-A, ranibizumab reduces oedema and limits visual loss or improves vision. Ranibizumab has a marketing authorisation for 'the treatment of visual impairment due to diabetic macular oedema in adults'.
- 2.2 The summary of product characteristics states that treatment should be given monthly and continued until maximum visual acuity is reached – that is, until visual acuity has been stable for 3 consecutive months. Thereafter, visual acuity should be monitored monthly. Treatment is resumed if monitoring indicates a loss of visual acuity caused by diabetic macular oedema, and continued until visual acuity has remained stable for 3 consecutive months. The interval between doses should not be shorter than 1 month.
- 2.3 Contraindications to ranibizumab include known hypersensitivity to the active substance or to any of its excipients, active or suspected ocular or periocular infections and active severe intraocular inflammation. Adverse reactions of treatment are mostly limited to the eye. Those commonly reported in clinical trials include vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, sensation of a foreign body in the eye, increased production of tears, blepharitis, dry eye, ocular hyperaemia, itching of the eye and increased intraocular pressure. Nasopharyngitis, arthralgia and headaches are also reported as common adverse reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.4 Ranibizumab costs may vary in different settings because of negotiated procurement discounts. The manufacturer of branded ranibizumab (Lucentis, Novartis) has agreed a patient access scheme with the Department of Health which makes ranibizumab available with a discount applied to all invoices. The size of the discount is commercial in confidence. The Department of Health

considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published. NHS England has completed a national procurement for medical retinal vascular medicines, which includes the biosimilar versions of ranibizumab. Prices paid for the originator or biosimilar ranibizumab should be in line with the national procurement outcome and should be no higher than that provided through the original patient access scheme.

3 The manufacturer's original submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of ranibizumab and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)). This document refers to an original submission and a revised submission (made during development of NICE technology appraisal guidance 237) and a rapid review submission, described for the first time in this document.

- 3.1 The manufacturer submitted evidence on the clinical effectiveness and cost effectiveness of ranibizumab monotherapy and ranibizumab plus laser photocoagulation compared with laser photocoagulation alone in its original submission. The manufacturer did not provide a comparison with bevacizumab, which the appraisal scope lists as a comparator. The manufacturer explained that this was because it believed that there is no robust evidence base for the clinical effectiveness or safety of bevacizumab in the treatment of diabetic macular oedema, bevacizumab has not been in long-term use in the NHS and there is no widely accepted dosage.

Clinical effectiveness

- 3.2 The manufacturer performed a systematic review of the evidence on the clinical effectiveness of ranibizumab. The review identified 4 randomised controlled trials (RCTs) that included ranibizumab in people with diabetic macular oedema – RESTORE, Diabetic Retinopathy Clinical Research Network Protocol I (DRCR.net), RESOLVE and READ-2. The manufacturer focused its submission on RESTORE and DRCR.net. The 2 other RCTs did not receive detailed attention, because the manufacturer judged them to be of less direct relevance to the decision problem. It stated that RESOLVE had limited application to the appraisal because it did not present a comparison with laser photocoagulation, which the manufacturer believed to be the most relevant comparator for an analysis concentrating on practice in the UK. The manufacturer stated that READ-2 did not provide high-quality evidence because follow-up was of shorter duration than in other

included studies, the schedule for treatment differed from that in the summary of product characteristics for ranibizumab and the manufacturer believed the trial may have had methodological shortcomings.

- 3.3 RESTORE was an industry-sponsored, multicentre (73 centres in 13 countries), sham-controlled randomised trial that compared ranibizumab plus sham laser photocoagulation (n=116) with ranibizumab plus laser photocoagulation (n=118) and laser photocoagulation plus sham injections (n=111). The trial lasted for 1 year, and participants were followed beyond 1 year, but did not necessarily remain on the treatment to which they had been randomised. RESTORE included people aged over 18 years with type 1 or type 2 diabetes and haemoglobin A1c (HbA1c) lower than 10% (86 mmol/mol). The trial protocol stated that, for each participant, only 1 eye should be treated, even if both eyes had disease. The eye with the worse vision was treated unless the investigator deemed it appropriate to treat the eye with the better vision. According to the trial protocol, 20% of participants had their better-seeing eye treated. Best corrected visual acuity (hereafter, 'visual acuity') was measured using 'ETDRS (Early Treatment Diabetic Retinopathy Study)-like' charts, in which a score of 85 letters corresponds to normal visual acuity ('20/20 vision'). An eye was eligible for randomisation if visual acuity was between 78 and 39 letters. Participants who had previous laser photocoagulation were included in the trial. Ranibizumab or sham injections were administered monthly in months 1 to 3; after this, they continued on a monthly basis until vision was stabilised for 2 visits or visual acuity reached 85 letters or more. Treatment with monthly injections was restarted if there was a decrease in visual acuity caused by progression of diabetic macular oedema and continued until the same criteria were fulfilled. Laser photocoagulation or sham laser photocoagulation was administered on day 1 and repeated at intervals of at least 13 weeks, if deemed necessary by the treating clinician. RESTORE was judged to satisfy all methodological quality criteria assessed by the manufacturer. At the time of the original submission, full details of RESTORE had not been published.
- 3.4 DRCR.net, an RCT funded by the US National Institutes of Health, was conducted at 52 clinical sites in the United States. The trial protocol stipulated that the trial would last for 3 years; however, at the time of submission for NICE technology appraisal 237, only 12-month follow-up data were available. Participants were aged over 18 years and had type 1 or type 2 diabetes. An eye was eligible for randomisation if it had centre-involving macular oedema and a visual acuity of

between 78 and 24 letters using the Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity test (again, a score of 85 letters corresponds to normal visual acuity). People who had previous laser photocoagulation were included in the trial. Randomisation was by eye (rather than by participant) and a participant could have both eyes involved in the study. Each eligible eye was randomised to receive either a sham injection plus laser photocoagulation (n=293 eyes), ranibizumab plus prompt laser photocoagulation (within 3 to 10 days of first ranibizumab injection; n=187 eyes) or ranibizumab with the possibility of subsequent (deferred) laser photocoagulation (at least 24 weeks after the first ranibizumab injection; n=188 eyes). In practice, only 28% of the ranibizumab plus deferred laser arm received laser treatment at any time during the first study year. A fourth group in DRCR.net received triamcinolone; this group is not included in this appraisal because triamcinolone is not currently used in clinical practice in the UK for diabetic macular oedema and was not in the scope for this appraisal. The randomisation protocol specified that, in participants with 2 eligible eyes, 1 eye would receive pharmacological treatment (plus prompt or deferred laser photocoagulation) and the other eye would receive prompt laser photocoagulation alone. Investigators administered ranibizumab or sham injections every 4 weeks until the fourth study visit (that is, after 12 weeks of treatment). At subsequent 4-weekly visits, the decision to give another injection depended on visual acuity and retinal thickness of the treated eye. Investigators repeated laser photocoagulation or sham laser photocoagulation, if needed, at intervals of at least 13 weeks (3-monthly). The manufacturer judged that DRCR.net satisfied all the methodological quality criteria it assessed (although it noted that participants randomised to ranibizumab plus deferred laser were aware of their allocated treatment).

- 3.5 The primary outcome measure of both RESTORE and DRCR.net was mean change in visual acuity in the treated eye after 12 monthly follow-up visits. The RESTORE analysis was based on the average of changes in visual acuity from baseline, measured monthly over the period from month 1 to month 12 ('mean average change'), whereas DRCR.net compared the visual acuity measured at baseline with that measured at 12 months ('mean change'). In RESTORE, the visual acuity of eyes randomised to ranibizumab monotherapy rose by a mean average of 6.1 letters, and eyes randomised to ranibizumab plus laser photocoagulation gained a mean average of 5.9 letters. In RESTORE, eyes randomised to laser photocoagulation alone gained fewer letters (0.8) than eyes randomised to either

ranibizumab-containing arm ($p < 0.001$). In DRCR.net, visual acuity rose by an average of 9 letters after 12 months in eyes randomised to ranibizumab plus either prompt or deferred laser photocoagulation compared with an average of 3 letters in eyes randomised to laser photocoagulation alone ($p < 0.001$ for either ranibizumab-containing arm compared with laser photocoagulation alone). The manufacturer provided a meta-analysis of mean changes from baseline visual acuity at 12 months combining results from RESTORE and DRCR.net. This suggested that the visual acuity of eyes treated with ranibizumab plus laser photocoagulation gained an average of 5.83 more letters than the visual acuity of eyes treated with laser photocoagulation alone (95% confidence interval [CI] 4.07 to 7.59, $p < 0.001$; fixed-effects and random-effects models estimate identical results).

- 3.6 In both RESTORE and DRCR.net, a series of subgroup analyses examined the primary outcome measure in participants categorised according to baseline characteristics. In all subgroups analysed in both trials, the visual acuity of participants randomised to ranibizumab-containing treatment improved more than the visual acuity of those randomised to laser photocoagulation. The manufacturer's submission noted that, in RESTORE, gains in visual acuity associated with ranibizumab were greatest in participants with baseline central retinal thickness of 300 micrometres or more and participants with a baseline visual acuity of fewer than 74 letters; the manufacturer presented no evidence on the statistical significance of these differences.
- 3.7 An alternative approach to presenting the results of visual acuity testing reports the proportion of participants in whom the treated eye improved or worsened by an amount reflecting a clinically significant change in vision, usually a gain or loss of 10 letters. The manufacturer's submission reported that, in RESTORE, the proportions of participants gaining 10 letters in visual acuity in their treated eye after 12 months of treatment were 37% in those randomised to ranibizumab monotherapy, 43% in those randomised to ranibizumab plus laser photocoagulation and 15% in those randomised to laser photocoagulation alone ($p < 0.001$ for either ranibizumab-containing arm compared with laser photocoagulation alone; p-values taken from European Medicines Agency Assessment Report). The proportions of participants who lost 10 letters of visual acuity in their treated eye after 12 months were 3%, 4% and 13% respectively ($p < 0.05$ for either ranibizumab-containing arm compared with laser

photocoagulation alone; p values calculated by the NICE technical team). In DRCR.net, after 12 months of treatment a gain of 10 letters in visual acuity was reported in 47% of eyes treated with ranibizumab plus deferred laser photocoagulation, 51% of eyes treated with ranibizumab plus prompt laser photocoagulation and 28% of eyes treated with laser photocoagulation alone ($p < 0.001$ for either ranibizumab-containing arm compared with laser monotherapy). After 12 months a loss of 10 letters in the treated eye was reported in 3%, 3% and 13% of eyes respectively ($p \leq 0.001$ for either ranibizumab-containing arm compared with laser photocoagulation alone). The manufacturer provided a meta-analysis of categorical visual acuity data from RESTORE and DRCR.net after 12 months of treatment. This suggested that the visual acuity of eyes randomised to ranibizumab plus laser photocoagulation was approximately twice as likely to improve by 10 letters than the visual acuity of eyes randomised to laser photocoagulation alone (relative risk=2.15, 95% CI 1.43 to 3.22, $p < 0.001$; random-effects model; fixed-effects model produced similar results). Eyes treated with ranibizumab plus laser photocoagulation were over 3 times less likely to lose 10 letters in visual acuity (relative risk=0.28, 95% CI 0.15 to 0.53, $p < 0.001$; random-effects model; fixed-effects model produced similar results).

- 3.8 RESTORE measured vision-related quality of life using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), which has 25 questions designed to measure the effect of visual impairment on daily functioning and quality of life. The mean changes from baseline in the composite score and in subscales related directly to vision were in favour of ranibizumab compared with laser photocoagulation alone ($p < 0.05$), but benefit was not demonstrated in subscales addressing dependency and driving ($p > 0.05$). The RESTORE investigators also administered assessments of health-related quality of life, including EuroQol-5D (EQ-5D). The manufacturer did not report the results directly, although its economic model relied on an analysis incorporating the EQ-5D data (see section 3.12).
- 3.9 The manufacturer stated that ranibizumab has a favourable safety profile, emphasising that extensive evidence is available from the use of ranibizumab in the treatment of wet age-related macular degeneration. Although none of the RCTs of ranibizumab in diabetic macular oedema were designed primarily to assess safety outcomes, no significant differences were observed between arms in the frequency of ocular and non-ocular adverse events. None of the studies

reported death rates.

Cost effectiveness

- 3.10 The economic evidence provided by the manufacturer in its original submission comprised a brief literature review (identifying no relevant published analyses) and a de novo cost–utility analysis. The cost–utility analysis used a Markov model simulating cohorts of people with diabetic macular oedema receiving ranibizumab monotherapy, ranibizumab plus laser photocoagulation, or laser photocoagulation alone. The model had 3-monthly cycles and a base-case time horizon of 15 years. It assumed (simulated) a starting population with diabetic macular oedema with a mean age of 63 years and visual acuity scores of between 75 and 36 letters. Health states were defined by visual acuity in the treated eye, rather than both eyes, and used 10-letter categories (with the exception of the best and worst states), resulting in 8 health states excluding death: 0 to 25 letters, 26 to 35 letters, 36 to 45 letters, 46 to 55 letters, 56 to 65 letters, 66 to 75 letters, 76 to 85 letters and 86 to 100 letters.
- 3.11 Based on the average number of injections received in RESTORE, the manufacturer's original model included 7 ranibizumab injections in the first year for both the ranibizumab monotherapy arm and the combination therapy arm. The manufacturer included an additional stopping rule, assuming that people with a visual acuity of 76 letters or more in the treated eye would not receive active treatment and would incur no treatment costs. In the second year of the model, based on data from DRCR.net, the manufacturer assumed 3 further ranibizumab injections in the ranibizumab monotherapy arm and 2 further ranibizumab injections in the combination therapy arm. For both the combination therapy arm and the laser photocoagulation alone arm, the model assumed 2 laser photocoagulation treatments in the first year and 1 additional laser treatment in the second year. The original model did not simulate any ranibizumab treatment or laser photocoagulation after the second year. The manufacturer accepted that, in practice, additional laser photocoagulation would take place after the second year, but assumed that there would be no difference between the modelled arms in this respect and therefore any costs and effects would cancel each other out.
- 3.12 To estimate the health-related quality of life associated with each health state

corresponding to vision in the model, EQ-5D data from RESTORE were transformed to utility values using standard social tariffs and then related to visual acuity in the treated eye using linear regression. In this way, a mathematical relationship was assumed between visual acuity in the treated eye and the health-related quality of life of people with diabetic macular oedema. Tests of interaction demonstrated that neither treatment allocation nor duration of treatment at the time of measurement had a significant impact on the relationship between utility and visual acuity category. Therefore, the utility value was derived for each visual acuity category using the whole data set, without any adjustment variables. The results of the regression suggested that, depending on visual acuity in the treated eye, the utility value ranged from 0.860 to 0.547. The utility value for the best health state (visual acuity 86 to 100 letters) resulting from the regression was 0.831; however, this result was considered anomalous, because it was based on relatively few data points and it was thought unrealistic that utility should be worse than in the next-best state, in which vision is inferior. Therefore, the manufacturer set the utility value for a visual acuity of 86 to 100 letters to be equal to the utility value for a visual acuity of 75 to 85 letters (that is, 0.860). The manufacturer did not apply any treatment-specific utilities and specifically did not apply a decrement in utility value to reflect adverse effects associated with the treatments.

- 3.13 Depending on the period of follow-up being simulated, the model used 3 different sets of data and assumptions to estimate the probability of changing between visual acuity states (transition probabilities). The first phase of the model reflected the first year of treatment, for which the manufacturer drew transition probabilities directly from changes in visual acuity observed among individual participants in RESTORE. In the original model, this data set included a proportion of treated eyes with a visual acuity of more than 75 letters at baseline, although eyes with equivalent vision were not simulated in the model. In the second and third phases of the model, the manufacturer based the transition probabilities on a 3-way matrix that reflected the estimated likelihood of improvement, deterioration or no change in the visual acuity of a given eye. The manufacturer assumed that the same probabilities applied to all states (with the exception of assuming that an eye with the best possible visual acuity could not improve and that an eye with the worst possible visual acuity could not worsen). The second phase of treatment reflected a period during which visual acuity was assumed to remain constant. This was based on the DRCR.net study, which the manufacturer

interpreted as showing that average visual acuity was maintained between 12 months and 24 months for all treatments. Therefore, the manufacturer assumed equal probabilities of improving or worsening in all model arms. In the original model, this phase comprised the second year of treatment only. In the third phase, the model assumed no treatment effect: based on an informal review of epidemiological literature, the manufacturer assumed quarterly probabilities of 0.025 for improvement and 0.035 for deterioration in all arms (implying that the probability of visual acuity staying the same was 0.94 in any quarter). In the original model, this final phase began at the start of year 3, and continued until the end of the model. According to this approach, the relative difference in treatment effect observed at the end of the initial treatment phase (year 1) was preserved for the remainder of the model. Thus, beyond 1 year, the visual acuities of participants previously treated with ranibizumab remained constant during the second year and after that declined at the same rate as the visual acuities of participants previously treated with laser photocoagulation. As a result, the relative difference in vision between treatments estimated at the end of the first year was preserved for the remainder of the model (that is, for the next 14 years).

- 3.14 In its model, the manufacturer assumed that the probability of dying is the same for all health states (so no additional risk of death was associated with worsening vision). Mortality rates were derived from life tables for England and Wales, modified by a relative risk representing the additional hazard of death for the modelled cohort when compared with the general population. In the original model, the manufacturer used a relative risk of 1.27, drawn from published literature comparing the risk of death for people with clinically significant diabetic macular oedema with the risk of death for people with diabetes, but without diabetic macular oedema. The manufacturer modelled adverse events on the basis of observed, treatment-specific rates of 4 events (cataract, endophthalmitis, retinal detachment and vitreous haemorrhage) in a pooled analysis of RESTORE and DRCR.net. The manufacturer included only the costs associated with these complications; it did not assume that the presence of these adverse events lowers quality of life (utility).
- 3.15 The cost of ranibizumab included in the original model was £761.20 per injection (this was before the manufacturer submitted a patient access scheme; the manufacturer submitted the patient access scheme after publication of the appraisal consultation document for NICE technology appraisal guidance 237, and

revised it for the rapid review submission). Unit costs of a visit to an eye clinic for a check-up and/or treatment were based on NHS reference costs (2008/09). The manufacturer assumed that treatment with both ranibizumab and laser photocoagulation occurs on an outpatient basis, and costs £150.00 per visit. For combination therapy, the manufacturer assumed that ranibizumab injections and laser photocoagulation would occur at the same visit, and cost £184.00 per visit. The manufacturer assumed that the full cost of laser photocoagulation is encompassed within the NHS reference cost for the clinic visit and included no additional costs for buying and maintaining the equipment. The costs (£126.00 each) of visits to monitor people (for vision and recurrence of disease) were also included: in the original model, people receiving ranibizumab monotherapy had 12 visits in the first year and 10 visits in the second year; people receiving combination therapy had 12 visits in the first year and 8 visits in the second year; those receiving laser photocoagulation alone in the first and second years, and all people from the third year onwards, had 4 visits per year. For the ranibizumab-containing arms, a visit for treatment was assumed to include monitoring as well. The same assumption was not applied for people receiving laser photocoagulation alone; that is, people receiving laser photocoagulation needed separate visits for treatment and monitoring.

- 3.16 In the model, the manufacturer applied estimated costs associated with severe vision loss for people with the lowest visual acuity in the treated eye (0 to 25 or 26 to 35 letters), regardless of vision in the non-treated eye. These costs reflected the additional resource use associated with people who are eligible to register as severely sight impaired (blind). The costs accounted for a range of items including low-vision aids, rehabilitation, residential care, district nursing, community care and the cost of treating complications including depression and falls. The manufacturer drew cost data largely from a published costing study of blindness in the UK that focused on people with age-related macular degeneration (Meads and Hyde 2003), with costs updated or adjusted for inflation as appropriate. The total cost applied was £6067 in the first year and £5936 in subsequent years.
- 3.17 In its deterministic base case, the manufacturer's original model estimated an incremental cost-effectiveness ratio (ICER) of £19,075 per quality-adjusted life year (QALY) gained for ranibizumab monotherapy compared with laser photocoagulation alone. The model predicted that combining laser

photocoagulation with ranibizumab would be more expensive and less effective than ranibizumab alone; that is, ranibizumab alone dominated combination therapy. The manufacturer also presented a series of deterministic sensitivity analyses in which single parameters (or related groups of parameters) were varied across plausible ranges. These analyses suggested that the model was most sensitive to the time horizon: when the time horizon was limited to 10 years, the estimated ICERs for ranibizumab monotherapy compared with laser photocoagulation alone rose by approximately 50%, to £30,367 per QALY gained. Most sensitivity analyses repeated the base-case finding that ranibizumab monotherapy dominates combination therapy with ranibizumab plus laser photocoagulation. Probabilistic sensitivity analysis (based on 10,000 Monte-Carlo simulations) suggested that the probability of ranibizumab monotherapy providing best cost–utility compared with laser alone was 49.3% and 76.8% at thresholds of £20,000 and £30,000 per QALY gained respectively. The probability of combination therapy providing best cost–utility compared with ranibizumab monotherapy was 19.4% and 17.8% at the same thresholds (these estimates have been corrected from the manufacturer's submission for NICE technology appraisal guidance 237 by the NICE technical team and verified by the ERG).

3.18 The manufacturer also presented a series of deterministic subgroup analyses in which first-year transition probabilities were derived from analyses of the RESTORE trial limited to participants with the characteristic(s) in question. The manufacturer changed no other parameters in the model. The manufacturer noted that several of the analyses were based on small numbers of participants. There were large variations between the results of some subgroups:

- Limiting the analysis to people with good glycaemic control (HbA1c less than 8%) produced an ICER of £13,196 per QALY gained for ranibizumab monotherapy compared with laser photocoagulation. In people with poorer glycaemic control (HbA1c 8% or more) ranibizumab monotherapy had an ICER of £36,383 per QALY gained when compared with laser photocoagulation.
- In people who previously had laser photocoagulation, ranibizumab monotherapy was associated with an ICER of £29,660 per QALY gained compared with laser photocoagulation. The equivalent figure for the subgroup who had not previously had laser photocoagulation was £12,675 per QALY gained.

- The ICERs for ranibizumab monotherapy compared with laser photocoagulation in people with baseline visual acuity of 36 to 45 letters, 46 to 55 letters, 56 to 65 letters and 66 to 75 letters were £52,704, £7645, £42,477 and £12,198 per QALY gained respectively.

However, the manufacturer considered that in light of the limitations related to the small number of trial participants in some of the subgroups, the relative cost effectiveness of ranibizumab monotherapy in these subgroups is uncertain and should be interpreted with caution.

Evidence Review Group comments on the manufacturer's original submission

- 3.19 The ERG noted that the manufacturer's original submission did not contain a comparison of ranibizumab with bevacizumab, which the appraisal scope lists as a comparator. The ERG report stated that, although it does not have a marketing authorisation for use in diabetic macular oedema in the UK, bevacizumab is used by ophthalmologists in some NHS centres if laser photocoagulation has failed to produce a response or as an alternative treatment if long-term treatment with laser photocoagulation is considered a risk. The ERG questioned the manufacturer's argument that there is a lack of robust evidence on clinical effectiveness or safety of bevacizumab in the treatment of diabetic macular oedema. In its report, the ERG provided details of 29 published studies it considered relevant to the use of intraocular bevacizumab in diabetic macular oedema, including 7 randomised comparisons with laser photocoagulation and/or sham injections. The ERG noted that some of the evidence evaluates the long-term effects of bevacizumab and some compares different dosages. The ERG stated that the manufacturer's view of bevacizumab was 'unjustifiably negative' and expressed the opinion that the evidence base should have been sufficient to enable an indirect comparison of ranibizumab with bevacizumab.

Additional evidence to the original submission submitted by the manufacturer during consultation for NICE technology appraisal guidance 237

- 3.20 In response to consultation on the original appraisal consultation document, the manufacturer submitted a revised cost–utility analysis, addressing reservations the Committee had expressed about the original model and submitted a first patient access scheme. Several consultees and commentators, including patient and professional groups, agreed with the Committee that the manufacturer's original economic model had given an unrealistic representation of likely clinical practice in some respects.
- 3.21 The manufacturer stated that the revised model should be 'considered a better-seeing eye model' – that is, it should be thought of as simulating a treatment strategy in which people with diabetic macular oedema received treatment in their better-seeing eye only. This was a change from the manufacturer's original economic analysis, in which the modelled treatment strategy assumed that people would largely receive treatment in their worse-seeing eye. The manufacturer observed that cost–utility models produce lower ICERs when simulating treatment in the better-seeing eye of people with diabetic macular oedema than when simulating treatment in the worse-seeing eye. This is partly because the health-related quality of life of people with visual impairment is associated primarily with vision in the better-seeing eye and partly because the costs of severe visual impairment depend on vision in the better-seeing eye. Thus, in general, treatments that maintain or improve vision in the better-seeing eye will be favoured in economic analyses. The manufacturer cited the precedent of [NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#) in which the Assessment Group's model had explicitly assumed that only the better-seeing eye was treated, but the Committee had made recommendations on the assumption that treatment would be given to the first eye to present clinically, be it the better- or worse-seeing eye. For these reasons, the manufacturer felt it would be helpful to present the Committee with a model that explicitly assumed treatment of the better-seeing eye, although the data on which the model was based were drawn predominantly from people whose worse-seeing eye had been treated, and it did not otherwise change the way the model associated vision in the worse-seeing

eye with quality of life.

- 3.22 The manufacturer accepted the view the Committee had expressed in the appraisal consultation document that its original model had underestimated the hazard of death associated with diabetic macular oedema by not including the hazard associated with diabetes itself. Its revised model used a higher relative risk of death of 2.45 for people with diabetic macular oedema compared with the general population. The manufacturer derived this value by combining an estimate of the additional hazard of death associated with diabetes (1.93 compared with the general population, from an English epidemiological study by Mulnier et al. 2006) with an estimate of the additional hazard of death independently associated with macular oedema among people with diabetes in Wisconsin, USA (1.27, as reported by Hirai et al. 2008). The manufacturer stated that the revised relative risk of 2.45 was more plausible, although it might overestimate the true hazard associated with diabetic macular oedema. It noted that the revised model predicted that 43% of the cohort would remain alive after 15 years (at age 78), whereas the original model had suggested that 65% of people would be alive at that time.
- 3.23 In NICE technology appraisal guidance 237 the Committee considered at its first meeting that, by assuming people whose visual acuity rose to 76 letters or higher would stop receiving ranibizumab, the manufacturer's original model had not reflected likely clinical practice. Acknowledging this view, the manufacturer removed the stopping rule from the base case of its revised model. For related reasons, the manufacturer also revised the effectiveness evidence used to simulate the first year of treatment. The original model drew transitions between visual acuity states from those observed in the whole population in RESTORE, including participants whose visual acuity had been higher than 75 letters at the start of treatment. In its revised model, the manufacturer calculated visual acuity state transitions in the first year of treatment using only participants whose visual acuities matched those of the assumed starting population in the model (that is, only people with baseline visual acuities of 36 to 75 letters).
- 3.24 The manufacturer accepted that there were uncertainties around the assumption in its original model that people would need only 2 years of treatment with ranibizumab. Its revised model assumed that people receiving ranibizumab would receive an average of 2 injections in a third year of treatment and 1 injection in a

fourth year of treatment. In the laser photocoagulation arm, the model assumed once-yearly treatments for years 3 and 4. To reflect the benefit that would accrue from these additional treatments, the manufacturer extended its original assumption that visual acuity would be maintained in all arms in year 2 of the model to encompass years 3 and 4 – that is, vision remained stable from years 2 to 4 and then declined equally in the group treated with ranibizumab and the group treated with laser photocoagulation.

- 3.25 When considering the manufacturer's original model, the Committee had expressed concern that it did not account for the need to treat both eyes in a significant proportion of people. The manufacturer did not alter its base case to address this issue. However, it provided a scenario analysis, using its revised model, which simulated treatment in both eyes for 35% of people. This analysis assumed that, in people with bilateral disease, both eyes would be treated and monitored at the same visit, with ranibizumab drug and treatment costs doubled. The analysis applied reduced costs associated with severe visual impairment because fewer people would go blind in both eyes. The analysis assumed that treating the second eye would result in utility gains a quarter the magnitude of those achieved by treating the first eye; this is because the health-related quality of life of people who can see well with both eyes is only a little better than the health-related quality of life of people who can see well with 1 eye. The model calculated this figure by applying a 25% uplift to the QALYs generated by ranibizumab.
- 3.26 In NICE technology appraisal guidance 237, the Committee had noted that the range of utility values used in the manufacturer's original model was broader than would be expected according to the assumptions of the model. The Committee had suggested that 1 possible explanation for this was that the regression model used to define the relationship between visual acuity and utility (see section 3.12) had not accounted for confounding variables reflecting the effect of diabetic comorbidities on health-related quality of life. To address this point, the manufacturer's consultation comments included an 'extended' analysis, which re-estimated the relationship between visual acuity and utility using a model containing additional covariates: age, sex, duration of diabetes, blood pressure control at baseline (categorised dichotomously), baseline HbA1c and a variable indicating whether each treated eye was the participant's better- or worse-seeing one. This analysis suggested that, apart from visual acuity, only sex was a

significant predictor of utility ($p < 0.05$). The manufacturer concluded that the utility function used in the original model had not been confounded by factors relating to diabetic comorbidities and retained the same utility values in its revised base case. However, the manufacturer also presented a scenario analysis that used the utility values estimated in the extended regression analysis, including all non-significant covariates.

- 3.27 When considering the manufacturer's original model, the Committee had questioned the validity of assuming that the relative improvement in vision achieved in the first year would persist for the duration of the model (see section 3.13), that is, that vision would deteriorate equally in the groups. The manufacturer responded to this point in its consultation comments, arguing that there was no evidence to suggest that gains in visual acuity would diminish at different rates depending on the treatment. It also cited the precedent of [NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#), in which the Committee had accepted an analogous approach, as a reasonable basis for decision-making.
- 3.28 In NICE technology appraisal guidance 237, the Committee had expressed concern that the unit cost of injection procedures used in the manufacturer's original model (£150.00; see section 3.15) might underestimate the true costs of administering ranibizumab. In its response to consultation, the manufacturer provided a 'bottom-up' estimate of the cost of an intravitreal injection visit, compiling separate estimates of the costs associated with consulting individual members of an ophthalmology clinic team and including overheads. This resulted in an estimated unit cost of £142.91, which the manufacturer took as evidence that the value used in the original model had accurately reflected the administration costs of ranibizumab. The manufacturer emphasised that charges applied to visits for ranibizumab injections are subject to local agreements between commissioners and providers, and may not always reflect the true costs of service delivery.
- 3.29 In NICE technology appraisal guidance 237, the Committee had initially concluded that the manufacturer's original model overestimated the cost savings of ranibizumab-based therapy that would be achieved by avoiding or delaying severe vision loss. The model drew the costs of severe vision loss from visual acuities that fell below 35 letters in treated eyes, but the data sources from which

the manufacturer drew these costs used visual acuity in the better-seeing eye. By stating that its revised model should be considered to simulate treatment in the better-seeing eye, the manufacturer suggested it had removed this problem.

- 3.30 The results of the manufacturer's revised model in NICE technology appraisal guidance 237 included a subgroup analysis estimating the cost–utility of ranibizumab in people with the greatest degree of macular oedema (central foveal thickness greater than 400 micrometres). The manufacturer provided this analysis in response to comments from clinical specialists, reported in the original appraisal consultation document, suggesting that laser photocoagulation may be less effective in a thicker, more oedematous retina. For this reason, the manufacturer stated that such people represented a 'clinically plausible' subgroup in which ranibizumab could be expected to have a greater relative effect when compared with laser photocoagulation. The manufacturer confirmed that the trial protocol for RESTORE had pre-specified subgroup analyses according to 3 categories of central foveal thickness: less than 300 micrometres, 300 to 400 micrometres and greater than 400 micrometres. In its response to consultation, the manufacturer stated that it had carried out tests of the statistical significance of differences in clinical outcome according to baseline central foveal thickness category. However, the results of these tests were not presented in the submitted documentation.
- 3.31 The manufacturer's revised model also included a patient access scheme reflecting its agreement with the Department of Health in 2011 that ranibizumab will be made available to the NHS at a discounted price (level of discount confidential; see [section 2.4](#)).
- 3.32 The manufacturer's revised base case focused solely on the comparison of ranibizumab monotherapy with laser photocoagulation. It estimated that ranibizumab is associated with an ICER of £30,277 per QALY gained (disaggregated cost and QALY estimates are unavailable because of the confidentiality of the patient access scheme). In the subgroup of people with central foveal thickness greater than 400 micrometres, the equivalent ICER was £21,418 per QALY gained.
- 3.33 The manufacturer's scenario analysis simulating treatment in both eyes for 35% of people resulted in an ICER of £44,355 per QALY gained for ranibizumab

monotherapy compared with laser photocoagulation. In the subgroup of people with central foveal thickness greater than 400 micrometres, the equivalent ICER was £35,719 per QALY gained.

- 3.34 The manufacturer provided a scenario analysis adopting utilities re-estimated from RESTORE data using an extended model with additional covariates reflecting baseline characteristics of participants and factors relating to diabetic comorbidities (see section 3.26). This resulted in an increase in the ICER from its base case of £30,277 per QALY gained to £33,857 per QALY gained for ranibizumab monotherapy compared with laser photocoagulation.
- 3.35 A further series of scenario analyses adopted alternative estimates of utility drawn from various published sources. When utility values from the better-seeing eye study by Lloyd et al. were used, the ICER was £24,779 per QALY gained. When utility was estimated according to an equation published by Sharma et al., associating visual acuity in the better-seeing eye with health-related quality of life, the ICER was between £12,312 and £12,610 per QALY gained, depending on the version of the equation used. A final analysis adopted utility values estimated in a study by Czoski-Murray et al. (referred to as Brazier et al. in NICE technology appraisal guidance 237), in which members of the general public valued levels of visual impairment that were simulated by custom-made contact lenses, using the time trade-off method. Participants wore the same lenses in both eyes, so the resulting utility values reflected bilateral impairment of vision. This was the source of utility values the Committee had judged most accurately reflected the health-related quality of life associated with visual impairment in [NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#). When these values were used in the revised ranibizumab model, the ICER was £23,664 per QALY gained. This ICER has been amended from the ICER given in the manufacturer's consultation comments to correct an error in the utility values used (identified by the NICE technical team and confirmed by the manufacturer in correspondence).
- 3.36 In its response to consultation on the appraisal consultation document for NICE technology appraisal guidance 237, the manufacturer provided additional arguments on the suitability of bevacizumab as a comparator. The manufacturer stated that bevacizumab could not be considered routine or best practice, because NHS experience is 'limited to experimental or compassionate use' and

'there are no robust data to demonstrate the safety, effectiveness and quality of the product'. The manufacturer argued that the optimum dose of bevacizumab for intraocular use is not established. It summarised 'emerging safety signals for the use of unlicensed intravitreal bevacizumab', and emphasised that any cost–utility analysis including bevacizumab would have to include the costs of an NHS pharmacovigilance programme. The manufacturer also reviewed the evidence that might be used to perform an indirect comparison of ranibizumab with bevacizumab. It concluded that significant methodological and clinical differences between studies precluded a valid analysis.

Evidence Review Group's comments on the manufacturer's revised model during NICE technology appraisal guidance 237

- 3.37 The ERG reviewed the manufacturer's consultation comments and revised economic model. It stated that the revised model's updated estimate of the relative risk of death for people with diabetic macular oedema compared with the general population (relative risk 2.45; see section 3.22) was reasonable. It agreed with the manufacturer that this figure may be an overestimate of the true additional hazard associated with diabetic macular oedema, but emphasised that it was a more realistic figure than that used in the original model.
- 3.38 The ERG noted the modified assumptions about duration of treatment in the manufacturer's revised model (see section 3.24). It had no comments about the manufacturer's new assumptions about additional treatments in years 3 and 4 of the model. However, the ERG emphasised that significant uncertainty remained about whether people with diabetic macular oedema would need injections of ranibizumab beyond the fourth year of treatment.
- 3.39 The ERG reviewed the manufacturer's scenario analysis as part of its revised model, which assumed that 35% of people with diabetic macular oedema would need treatment in both eyes (see section 3.25). It noted that the assumed benefit of treatment in the second eye (a 25% uplift in incremental QALY gain) did not appear to be evidence-based. It also expressed the view that, in people in whom the better-seeing eye is treated, the other eye would receive the same therapy unless it had already suffered irreparable visual loss. As a result, the ERG suggested that an ophthalmologist is likely to offer treatment in both eyes or only

the worse-seeing eye.

- 3.40 The ERG reviewed the manufacturer's comments about the utility values used to estimate health-related quality of life in its revised model, and its additional analyses exploring alternative assumptions. The ERG expressed continuing concern that the analyses did not account for the covariance between visual acuity in the treated and untreated eyes of participants at baseline – that is, it was possible that health-related quality-of-life measurement was strongly influenced by vision in the untreated eye, which was unlikely to be similar to vision in the treated eye. The ERG suggested that it would have been possible to avoid this problem by basing the regression model on the impact over time of treatment on utility – that is, by modelling the relationship between changes in visual acuity and changes in health-related quality of life, rather than modelling absolute levels of both.
- 3.41 The ERG stated that the bottom-up costing exercise carried out by the manufacturer to validate the unit cost of ranibizumab injection procedures (see section 3.28) was reasonable and useful. It noted that, if the additional cost of consumables (instruments, cotton wool, a drape and a syringe) were included, the total estimate would reach the £150 unit cost used in the model. The ERG expressed support for the manufacturer's assumption that all ranibizumab injections would take place on an outpatient basis.
- 3.42 The ERG reviewed the manufacturer's subgroup analysis presenting the cost-utility of ranibizumab in people with central foveal thickness greater than 400 micrometres. It accepted the theoretical basis of the subgroup, agreeing that laser photocoagulation is expected to be less effective in a very thick retina. Because it noted that the manufacturer had presented subgroup results only for people with the thickest retinas, the ERG provided equivalent data for the other categories of retinal thickness analysed in RESTORE. For people with central foveal thickness less than 300 micrometres (49 trial participants), the ICER for ranibizumab compared with laser photocoagulation was £27,496 per QALY gained. For people with central foveal thickness of 300 to 400 micrometres (62 trial participants), the ICER for ranibizumab compared with laser photocoagulation was £386,321 per QALY gained. The ERG noted that this pattern of cost-effectiveness estimates was erratic and should be interpreted with caution. It commented that the calculations were based on small sample

sizes, although it noted that the subgroup presented by the manufacturer – people with central foveal thickness greater than 400 micrometres (see section 3.32) – represented around half of the population recruited in RESTORE (114 of 217 participants randomised to ranibizumab monotherapy or laser photocoagulation).

- 3.43 The ERG noted that the manufacturer's model (in both its original and revised versions) assumed that an administration visit for a ranibizumab injection can double as a monitoring visit but an administration visit for laser photocoagulation cannot. The ERG provided analyses removing this difference. When it was assumed that people receiving ranibizumab need additional monitoring visits (as for laser photocoagulation), the ICER rose to £37,673 per QALY gained; when it was assumed that people receiving laser photocoagulation do not need additional monitoring visits (as for ranibizumab), the ICER was £33,074 per QALY gained.
- 3.44 The ERG responded to the manufacturer's comments on the suitability of bevacizumab as a comparator. It disagreed with the manufacturer's suggestion that the optimum dose of bevacizumab is unknown, suggesting that the standard dose is 1.25 mg. The ERG reiterated its view that safety data are available on the use of bevacizumab. It emphasised that the incidence of adverse events is low with both ranibizumab and bevacizumab. The ERG noted that a recent head-to-head trial of ranibizumab and bevacizumab for age-related macular degeneration (CATT [Comparison of Age-related Macular Degeneration Treatments Trial]) showed equivalent efficacy between the 2 technologies.

Rapid review of NICE technology appraisal guidance 237 patient access scheme

- 3.45 NICE technology appraisal guidance 237 did not recommend ranibizumab for the treatment of visual impairment due to diabetic macular oedema. After publication of NICE technology appraisal guidance 237, the manufacturer submitted a revised patient access scheme in which it applied a revised discount to ranibizumab for all indications (see [section 2.4](#)) to be considered as a rapid review of the original guidance.

3.46 As this was a rapid review, the manufacturer did not submit any additional clinical effectiveness data. However, in addition to the revised patient access scheme, the manufacturer submitted an amended economic model that attempted to address 6 specific concerns that were raised by the Committee in section 4.29 of NICE technology appraisal guidance 237 as follows:

- By not accounting for the need to treat both eyes in a large proportion of people with diabetic macular oedema, the manufacturer's revised base-case model underestimated the benefits and – to a greater degree – the costs of treatments. The manufacturer's scenario analysis simulating treatment in both eyes for 35% of people provided a more realistic reflection of likely clinical practice.
- The range of utility values used in the manufacturer's revised base case was broader than would be expected according to the assumptions of the model. The Committee preferred the manufacturer's scenario analysis adjusting for factors that may influence the relationship between visual acuity and health-related quality of life.
- The model underestimated the amount of ranibizumab that people with diabetic macular oedema were likely to need over time. Basing the number of injections for year 2 of the model's ranibizumab monotherapy arm on experience in DRCR.net overlooks the fact that the participants in the trial also received laser photocoagulation, which clinicians believe may have a ranibizumab-sparing effect. The declining number of ranibizumab injections assumed in years 3 and 4 is not evidence-based, and is unlikely to lead to stable vision during that period, as assumed. It may also have been unrealistic to assume that ranibizumab treatment will not continue beyond 4 years.
- The model's assumption that the relative benefit achieved during the treatment phase lasts indefinitely was unrealistic. If [NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#) is considered as a precedent, then it should be noted that the model in that appraisal had a shorter time horizon, which limited the Committee's uncertainty about extrapolating treatment effects into the future.
- The model applied unequal assumptions about treatment and monitoring

visits for people treated with ranibizumab and those treated with laser photocoagulation.

- The manufacturer's model overestimated the degree of glycaemic control that would be expected in people treated in clinical practice in the UK.

3.47 In response to the Committee's concerns, the manufacturer amended its economic model with the following revisions:

- To approximate an ICER for treating both eyes, the manufacturer multiplied the ICER from the revised model, considered by the manufacturer to represent a better-seeing eye model, by a factor of 1.5. The manufacturer noted that this approach was consistent with that taken by the Committee in [NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#), when it observed that 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 treating only the better-seeing affected eye. The manufacturer did not make any additional changes to the model to address this issue.
- To address the Committee's concerns about utility, the manufacturer considered that the utility values estimated in a study by Czoski-Murray et al. (2009) were those preferred by the Committee. In this study, the investigators developed a regression model that estimated the contribution of visual acuity (measured by the LogMAR [logarithm as the minimal angle of resolution] scale) to health-related quality of life, adjusting for age. The regression model was subsequently used by the manufacturer to estimate utility values for each of the 8 visual acuity health states (defined by the ETDRS scale) after converting the upper and lower limits of the ETDRS scale to its LogMAR equivalent. Based on a mean age of 65 years, the estimated utility values used in the manufacturer's new base-case analysis ranged from 0.869 for the best health state to 0.353 for the worst health state.
- To address the Committee's concerns about the number of ranibizumab injections people with diabetic macular oedema would need, the manufacturer assumed that people receiving ranibizumab alone would need a total of 14 ranibizumab injections over 4 years: 7 injections in the first year, 4 injections in the second year, and 3 injections in the third year. These

assumptions were based on a 2-year extension of the RESTORE study, which showed that trial participants needed a decreasing number of ranibizumab injections from the first year to the third year. The manufacturer assumed that no injections were needed in the fourth year. The manufacturer also carried out a threshold analysis to estimate the maximum number of ranibizumab injections that could be administered over the time horizon of the model while maintaining an ICER below £30,000 per QALY gained.

- To address the Committee's concerns about extrapolating the relative benefit of treatment with ranibizumab beyond the initial treatment phase, the manufacturer reduced the time horizon of the model from 15 years to 10 years. The manufacturer also conducted a threshold analysis to explore the highest rate at which vision could worsen in people treated with ranibizumab and maintain an ICER below £30,000 per QALY gained. To do this, the manufacturer assumed from the fourth year onwards, quarterly probabilities of 0.025 for improvement and 0.055 for deterioration for people receiving ranibizumab monotherapy and quarterly probabilities of 0.025 for improvement and 0.035 for deterioration for people receiving laser photocoagulation alone.
- To address the Committee's concerns about care provided during visits to the eye clinic, the manufacturer assumed that for people receiving either ranibizumab monotherapy or laser alone, a visit for treatment also included monitoring. People receiving ranibizumab monotherapy visited the eye clinic 12 times in the first year, 8 times in the second year and 6 times in the third year; those receiving laser photocoagulation alone had 4 visits per year in the first, second and third years, and people on either treatment had 2 visits per year in the fourth year.
- Despite the Committee's concerns that the ICER for ranibizumab monotherapy compared with laser photocoagulation would be higher in people with poor glycaemic control, the manufacturer did not present further subgroup analyses according to the degree of glycaemic control. The manufacturer noted the Committee's considerations in NICE technology appraisal guidance 237 that analyses restricted to people with good glycaemic control (HbA1c less than 8%) and poor glycaemic control (HbA1c 8% or more) were 'exploratory'. The manufacturer also suggested that these subgroup analyses need careful interpretation because of the small sample

sizes, which resulted in a very small number of people in extreme health states influencing the results.

- 3.48 The manufacturer's model for the rapid review submission, including the revised patient access scheme, compared ranibizumab monotherapy with laser photocoagulation. The manufacturer presented separate ICERs for treating the better-seeing eye and for treating both eyes. In the base case, the manufacturer estimated that treating the better-seeing eye with ranibizumab was associated with an ICER of £14,137 per QALY gained and that treating both eyes with ranibizumab was associated with an ICER of £21,205 per QALY gained. The manufacturer estimated that an additional 4 injections of ranibizumab can be given in years 4 to 9 (resulting in a total of 18 injections) for the ICER when treating both eyes to remain below £30,000 per QALY gained. The manufacturer also estimated that the rate of deterioration in vision (visual acuity) for people treated with ranibizumab in both eyes from year 4 onwards would need to be more than 1.5 times higher than that for people treated with laser photocoagulation for the ICER to increase to £30,000 per QALY gained. The manufacturer conducted one-way sensitivity analyses that suggested that the model was most sensitive to changes to the time horizon and to utility values. When the time horizon was limited to 5 years the ICER associated with treating both eyes was £41,568 per QALY gained. When the manufacturer instead used utility values from the study by Lloyd et al. (representing the contribution to utility from the better-seeing eye), the ICER associated with treating both eyes was £43,716 per QALY gained. The manufacturer provided no probabilistic sensitivity analyses in its rapid review submission.
- 3.49 To address the Committee's concerns about the validity of the manufacturer's previous subgroup analyses (submitted in response to the consultation on the original appraisal consultation document for NICE technology appraisal guidance 237) according to retinal thickness and the inconsistent relationship between retinal thickness and cost effectiveness, the manufacturer presented additional subgroup analyses according to the degree of retinal thickness. For the rapid review, the manufacturer presented subgroup analyses based on central retinal (rather than foveal) thickness, arguing that this more reliably measures retinal thickness than central foveal thickness. The manufacturer acknowledged that the pattern of cost-effectiveness estimates for the 3 subgroups defined by central foveal thickness had been erratic, and may have been influenced by small

sample sizes (see section 3.42). Therefore, the manufacturer combined the 2 subgroups with lower values of central retinal thickness to create 2 subgroups (less than 400 micrometres and 400 micrometres or greater) of similar size. The manufacturer presented post hoc tests of the statistical significance of differences in clinical outcome according to baseline central retinal thickness, which suggested that laser photocoagulation was less effective in people with central retinal thickness of 400 micrometres or more ($p < 0.01$) than in people with thicker retinas. In response to Committee comments in NICE technology appraisal guidance 237 that the manufacturer should explore subgroup-specific parameters for all model inputs, and not only effectiveness, the manufacturer also adjusted other model parameters according to the 2 subgroups, including distribution of visual acuity at baseline and treatment frequency in the first year. For people with central retinal thickness of 400 micrometres or more, the ICER associated with treating only the better-seeing eye was £8881 per QALY gained and the ICER associated with treating both eyes was £13,322 per QALY gained. For people with central retinal thickness of less than 400 micrometres, the ICER associated with treating the better-seeing eye was £28,861 per QALY gained and the ICER associated with treating both eyes was £43,292 per QALY gained.

ERG comments on the manufacturer's rapid review submission

- 3.50 The ERG reviewed whether the manufacturer had correctly implemented the revised patient access scheme in their cost-effectiveness analysis. Additionally, the ERG checked that the Committee's concerns about the manufacturer's revised model from the guidance on ranibizumab for diabetic macular oedema (NICE technology appraisal guidance 237) had been addressed in the economic analysis.
- 3.51 The ERG reported that the manufacturer addressed most of the issues raised by the Committee in NICE technology appraisal guidance 237. However the ERG raised the following concerns about the manufacturer's analyses:
- It was unclear why the manufacturer had reduced the number of injections from 1 to 0 in the fourth year of the model when it had increased the number of ranibizumab injections from 2 to 3 in the third year.
 - The ERG agreed with the manufacturer that the results of the manufacturer's

subgroup analyses by degree of glycaemic control may have been influenced by small sample sizes. However, the ERG suggested that the manufacturer could have addressed this issue in a probabilistic model rather than a deterministic analysis. When the ERG ran a probabilistic version of the manufacturer's model, for people with good glycaemic control (HbA1c less than 8%) it produced an ICER associated with the better-seeing eye of £12,895 per QALY gained for ranibizumab monotherapy compared with laser photocoagulation. In people with poorer glycaemic control (HbA1c 8% or more) ranibizumab monotherapy had an ICER associated with the better-seeing eye of £21,560 per QALY gained when compared with laser photocoagulation.

- The ERG commented that the manufacturer may have incorrectly converted the ETDRS scale to the LogMAR scale to establish utility values for 3 of the 8 visual acuity health states in the model. The ERG instead estimated utility values ranging from 0.850 for the best health state to 0.353 for the worst health state which, when applied in the manufacturer's model, slightly increased the ICERs for treating the better-seeing eye and both eyes to £14,473 and £21,710 per QALY gained respectively.

3.52 The ERG conducted exploratory analyses to determine whether the utility values used by the manufacturer were appropriate for people who only have their better-seeing eye treated. The ERG identified a study (Brown 1999) that measured vision-related utility values using the time trade-off method in 325 people from the USA with impaired vision (Snellen scale 20/40) in at least 1 eye. This study produced utility values reflecting the contribution of vision in the better-seeing eye to health-related quality of life that ranged from 0.920 to 0.540 for the 8 health states defined by visual acuity, a range the ERG noted was narrower than in the Czoski-Murray et al. study. The ERG noted that both studies showed a linear relationship between vision and utility. The ERG also noted from the Brown study that, among people who had good vision in their better-seeing eye, the worse-seeing eye contributed little to health-related quality of life.

3.53 To explore the impact of treating only the worse-seeing eye on health-related quality of life, the ERG presented 6 scenario analyses. The 2 extreme scenarios assumed that, at one extreme, treating only the worse-seeing eye and improving vision did not improve health-related quality of life, to the other extreme where

treating only the worse-seeing eye improves health-related quality of life to the same degree as would treating the better-seeing eye. The remaining 4 scenarios provided intermediate assumptions. The ERG used the range of utility values for the better-seeing eye from its own adjusted values estimated from Czoski-Murray et al. for the 8 health states reflecting the best to worst vision for the worse-seeing eye (a range of 0.497). The 6 scenarios explored the impact of vision in the worse-seeing eye on health-related quality of life using the following assumptions:

- Scenario analysis 1: A flat health-related quality-of-life function in which improvements in vision in the treated worse-seeing eye have no impact, that is, health-related quality of life is determined solely by vision in the untreated better-seeing eye.
- Scenario analysis 2: A health-related quality-of-life function in which treating only the worse-seeing eye results in 15% of the range of improvements in vision that would have been achieved by treating only the better-seeing eye, that is, a range of (15% of 0.497)=0.075.
- Scenario analysis 3: A health-related quality-of-life function in which treating only the worse-seeing eye results in 30% of the range of improvements in vision that would have been achieved by treating only the better-seeing eye, that is, a range of (30% of 0.497)=0.149.
- Scenario analysis 4: A health-related quality-of-life function in which treating only the worse-seeing eye results in 50% of the range of improvements in vision that would have been achieved by treating only the better-seeing eye, that is, a range of (50% of 0.497)=0.248.
- Scenario analysis 5: A health-related quality-of-life function in which treating only the worse-seeing eye results in 75% of the range of improvements in vision that would have been achieved by treating only the better-seeing eye, that is, a range of (75% of 0.497)=0.373.
- Scenario analysis 6: A health-related quality-of-life function in treating only the worse-seeing eye results in 100% of the range of improvements in vision that would have been achieved by treating only the better-seeing eye, that is, vision in the worse-seeing eye influences health-related quality of life to the same extent as vision in the better-seeing eye (range of 0.497).

3.54 The ERG also presented an alternative approach to estimating the costs and QALYs associated with treating both eyes. This differed from the manufacturer's approach of multiplying the ICER associated with treating the better-seeing eye by 1.5 to estimate the ICER associated with treating both eyes. The ERG made a number of assumptions about the proportion of people who would be treated in their better-seeing eye only, their worse-seeing eye only, or in both eyes and the associated costs and QALYs:

- To estimate the proportion of people who have only their better-seeing eye treated, the ERG based their estimate on the RESTORE trial, in which 20% of people had their better-seeing eye treated at baseline. The utility values used by the ERG were those associated with the better-seeing eye (from Czoski-Murray et al.). The ERG assumed that if vision in the better-seeing eye deteriorated to the point at which the person became severely visually impaired, the person incurs the costs associated with blindness.
- To estimate the proportion of people who have only their worse-seeing eye treated, the ERG based their estimate on the remainder of people who are treated only in their better-seeing eye or in both eyes ($100\% - 20\% - 35\% = 45\%$). The utility values used by the ERG were those associated with the health-related quality-of-life functions for treating the worse-seeing eye, as described in section 3.53. The ERG assumed that if vision in the worse-seeing eye deteriorated and the person became severely visually impaired, the person would not incur the costs associated with blindness, because the better-seeing eye continues to provide vision.
- The ERG assumed that 35% of people have both eyes treated based on figures presented by the manufacturer as part of its original submission for NICE technology appraisal guidance 237. The ERG assumed that changes in the vision of the worse-seeing eye contribute the same amount to health-related quality of life whether it is treated alongside the better-seeing eye or treated alone; that is, the 2 health-related quality-of-life functions resulting from changes in vision of the better-seeing eye or worse-seeing eye are independent. Therefore, the ERG calculated the total QALYs gained with ranibizumab treatment in both eyes as the total QALYs gained for improving vision of the better-seeing eye combined with the total QALYs gained for improving vision of the worse-seeing eye for each of the 6 scenarios described in section 3.53. The ERG assumed that treatment costs of

ranibizumab were doubled, and included the costs of blindness in the model. However, the ERG assumed that the costs of visits for treatment and for monitoring did not increase from the scenarios that considered treating only the better-seeing eye or worse-seeing eye.

- 3.55 The ERG then combined the total costs and QALYs for people treated in the better-seeing eye, the worse-seeing eye, or both eyes as a weighted average and calculated the resultant pooled ICERs for each of the 6 scenario analyses described in section 3.53. The ERG did not present subgroup analyses according to retinal thickness when using this approach to estimating the costs and QALYs associated with treating both eyes.
- 3.56 In these exploratory analyses, the ICERs ranged from £16,585 per QALY gained in scenario analysis 6 (changes in the vision of the worse-seeing eye have exactly the same impact on health-related quality of life as changes in the vision of the better-seeing eye) to £39,712 per QALY gained in scenario analysis 1 (changes in the vision of the worse-seeing eye were assumed to have no impact on health-related quality of life). The ERG repeated these analyses but replaced the utility values estimated from Czoski-Murray et al. with those from the study by Brown. This resulted in ICERs that ranged from £21,054 per QALY gained in scenario 6 to £50,879 per QALY gained in scenario 1. The ERG also repeated these exploratory analyses but increased the proportion of people receiving treatment in both eyes to 62% on the basis of the proportion of participants in the RESTORE trial with a best corrected visual acuity of 78 letters or fewer at baseline (the modelled threshold below which ranibizumab would be offered) in the second eye. When the ERG used utility values estimated from Czoski-Murray et al., the ICERs ranged from £15,433 to £29,868 per QALY gained; when the ERG used utility values from Brown, the ICERs ranged from £19,970 to £38,267 per QALY gained.
- 3.57 The ERG commented that based on the Brown study, which suggested that vision of the worse-seeing eye has minimal impact on a person's health-related quality of life, the ICERs from scenarios 4 to 6 (suggesting that vision in the worse-seeing eye contributes 50 to 100% to health-related quality of life) were less plausible than scenarios 1 to 3 (suggesting that vision in the worse-seeing eye contributes 0 to 30% to health-related quality of life). The ERG proposed that scenario 1 was implausible, because it was unlikely that vision in the worse-seeing eye would have no impact on health-related quality of life. In scenarios 2

and 3, the ICERs ranged from £32,843 to £27,999 per QALY gained when utility values estimated from Czoski-Murray et al. were used and from £42,227 to £36,089 per QALY gained when utility values from Brown were used. The ERG also commented that the scenarios that considered treating only the worse-seeing eye did not account for a gain in health-related quality of life from reducing the fear of blindness in the worse-seeing eye.

Additional analyses submitted by the manufacturer during consultation on the appraisal consultation document for the rapid review of NICE technology appraisal guidance 237

3.58 In response to the appraisal consultation document for the rapid review of NICE technology appraisal guidance 237, the manufacturer presented cost-effectiveness analyses based on the approach taken by the ERG when estimating the costs and QALYs associated with treating both eyes (see sections 3.53 to 3.54). The manufacturer presented alternative estimates, based on baseline data from RESTORE, of the proportion of people who would be treated in their better-seeing eye only, their worse-seeing eye only, or in both eyes. In addition, the manufacturer suggested that some patients in RESTORE were treated in an eye with the same vision as the other eye, defined as the same-seeing eye. The manufacturer defined a same-seeing eye as one with a difference in visual acuity between eyes of fewer than 5 letters on the ETDRS scale for patients with visual acuity of 50 letters or more in both eyes at baseline, or a difference in visual acuity of fewer than 10 letters for patients with visual acuity of fewer than 50 letters in both eyes at baseline. Based on these criteria, approximately 22% of patients from RESTORE were defined as being treated in the same-seeing eye, 22% were defined as being treated in the better-seeing eye and 56% were defined as being treated in the worse-seeing eye. The manufacturer presented 3 separate analyses, which varied the proportion of people who might be treated in their better-seeing eye only, their worse-seeing only, or in both eyes, to incorporate assumptions about treatment of same-seeing eyes:

- In the first analysis, the manufacturer assumed that treating the same-seeing eye improves health-related quality of life to the same degree as treating only the better-seeing eye. A total of 44% of people in RESTORE were treated in either the better-seeing eye or the same-seeing eye. Of the remaining 56% of

people, the manufacturer assumed that 35% were treated in both eyes and the remaining 21% were treated in the worse-seeing eye only.

- In the second analysis, the manufacturer defined the better-seeing eye as having a visual acuity of only 1 letter or more than the other eye, which suggested that the same-seeing eye had a visual acuity within 1 letter of the other eye. This resulted in 32% of people being treated in their better-seeing eye only, 35% treated in both eyes and the remaining 33% treated in their worse-seeing eye only.
- In the third analysis, the manufacturer assumed that the 22% of people defined as being treated in the same-seeing eye (based on a difference in visual acuity between eyes of fewer than 5 letters on the ETDRS scale for patients with visual acuity of 50 letters or more in both eyes at baseline, or a difference in visual acuity of fewer than 10 letters for patients with visual acuity of fewer than 50 letters in both eyes at baseline) would need treatment in both eyes in addition to the 35% of people already assumed to be treated in both eyes, resulting in 57% of people treated in both eyes. The manufacturer noted that this estimate was close to the proportion of participants in RESTORE with a visual acuity of 78 letters or fewer at baseline in both eyes. The manufacturer assumed that 32% of people would receive treatment only in their better-seeing eye on the basis of the better-seeing eye having a visual acuity better than the other eye by at least 1 letter. The remaining 11% were treated only in their worse-seeing eye.

3.59 For these 3 analyses, the manufacturer used utility values estimated from Czoski-Murray et al. and presented ICERs for scenarios 2 to 5 as defined by the ERG (see section 3.53), corresponding to an increasing impact on health-related quality of life from improved vision as a result of treating the worse-seeing eye. In analysis 1, the ICERs ranged from £17,332 per QALY gained in scenario 5 to £23,735 per QALY gained in scenario 2. In analysis 2, the ICERs ranged from £18,337 per QALY gained in scenario 5 to £27,679 per QALY gained in scenario 2. In analysis 3, the ICERs ranged from £16,978 per QALY gained in scenario 5 to £23,701 per QALY gained in scenario 2.

3.60 The ERG reviewed the new analyses provided by the manufacturer in response to the appraisal consultation document. The ERG commented that analysis 1, which assumed that 22% of people would be treated in their same-seeing eye only,

appeared to be unrealistic because if a patient had a same-seeing eye that needed treatment, then it was very likely that the other eye would also need treatment. The ERG also noted that in analysis 3, the manufacturer applied the criterion that defined what it assumed to be a minimum clinically relevant difference in visual acuity of fewer than 5 letters on the ETDRS scale when estimating the proportion of people treated in their same-seeing eye (22%), but did not apply this criterion when estimating the proportion of people treated only in the better-seeing eye (32%). Therefore, the ERG suggested that analysis 2, which did not include a minimum clinically relevant difference in visual acuity to define the same-seeing eye, defining it instead as an eye with vision equal within 1 letter, to be the most plausible of the 3 analyses presented by the manufacturer. The ERG repeated analysis 2, but replaced the utility values estimated from Czoski-Murray et al. with those from the study by Brown. This resulted in ICERs that ranged from £35,555 to £31,602 per QALY gained in scenarios 2 and 3, proposed as the 2 most plausible scenarios by the ERG.

- 3.61 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ranibizumab, having considered evidence on the nature of diabetic macular oedema and the value placed on the benefits of ranibizumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee understood from patient experts that visual impairment has a substantial negative impact on quality of life and activities of daily living in people with diabetic macular oedema. The patient experts placed particular emphasis on loss of independence and its implications for employment. They emphasised that diabetes is usually managed with self-care, and that visual impairment can affect a person's ability to manage their own condition (for example, checking their blood glucose level with a meter, administering medication, caring for their feet and managing their diet). The patient experts described a significant impact of visual impairment on emotional wellbeing, which can lead to depression and, in some instances, suicidal thoughts. The Committee understood that any relief from these problems would have a positive impact on the lives of people with diabetic macular oedema.
- 4.3 The Committee heard from the clinical specialists that the current standard treatment for diabetic macular oedema is focal and/or grid laser photocoagulation. The clinical specialists stated that an eye's response to laser photocoagulation is hard to predict but, in their experience, the people who benefit most tend to be those who have less visual impairment at the onset of treatment. People whose vision worsens despite laser photocoagulation are more likely to have thicker, more oedematous retinas. The clinical specialists explained that there are national screening programmes for diabetic retinopathy in England and Wales to identify people who need diagnosis and treatment.
- 4.4 The Committee discussed the likely place of ranibizumab in the treatment of diabetic macular oedema. It heard from the clinical specialists that they would consider using ranibizumab either on its own or in a treatment strategy including laser photocoagulation given before, after or at the same time as ranibizumab. The clinical specialists explained that they would be likely to start ranibizumab

treatment with a 'loading' period of monthly injections for at least 3 months. After this, they would monitor people on a regular basis, providing repeat monthly injections for as long as visual acuity improved and/or retinal thickness reduced (as measured using optical coherence tomography). The clinical specialists anticipated that people with diabetic macular oedema would need between 7 and 9 treatments in the first year. The Committee heard from the clinical specialists that treatment would not be for a predefined period. Instead, clinicians would discontinue treatment if a person's vision stopped improving, and would restart treatment in the event that the person's vision worsened. The clinical specialists stated that this phase would continue until it was evident that the person was deriving no additional benefit from treatment. The clinical specialists advised that they would carry out monthly follow-up in the first year of treatment, extending the interval to 6 to 8 weeks for people whose diabetic macular oedema stabilised. The clinical specialists gave the opinion that the RESTORE trial provided an accurate picture of likely clinical practice in this respect because it had followed a similar approach to treatment and monitoring (3-month loading followed by repeat injection at monthly intervals as deemed appropriate by the treating clinician). However, because people with diabetic macular oedema in clinical practice are likely to have more advanced visual impairment than those in clinical trials, they may also need more frequent treatment than observed in clinical trials.

- 4.5 The Committee heard from the clinical specialists that a clinically significant gain in visual acuity is 10 to 15 letters. However, the clinical specialists also stated that smaller gains could be significant – for example, if a gain were sufficient to allow a person to meet the legal requirements for driving. In general, the clinical specialists thought that a gain of 10 to 15 letters would benefit a person with worse vision more than a person with moderate visual impairment.
- 4.6 The Committee understood from the clinical specialists that, because diabetes is a systemic metabolic condition, diabetic macular oedema is more often seen in both eyes than maculopathy from other causes. The clinical specialists estimated that at least 25 to 30% of people with diabetic macular oedema need treatment in both eyes. The clinical specialists said that, for these people, they would aim to provide treatment in both eyes at the same visit. They explained that, through experience gained in treating wet age-related macular degeneration, many NHS units are now well equipped to treat people with ranibizumab. The clinical specialists suggested that ranibizumab treatment would need an ophthalmologist

(rather than a nurse) and would be provided on an outpatient basis.

- 4.7 The Committee heard from the clinical specialists that, if using visual acuity as part of a fixed algorithm for deciding whether and when to treat and re-treat, it would be vital to correct sight optimally before measuring visual acuity, and this would entail comprehensive refraction (correcting sight with lenses) on each occasion visual acuity was measured. In addition, clinics would need to use the same vision charts as used to test vision in the trials, which take considerably longer to administer than routine tests of visual acuity. The clinical specialists explained that both these factors would extend the time and resources needed for routine follow-up of people with diabetic macular oedema beyond what is needed in current clinical practice.
- 4.8 The Committee understood from the clinical specialists and patient experts that ranibizumab is generally well tolerated, and that people usually use antibiotic eye drops for a few days after treatment with ranibizumab to prevent infection.

Clinical effectiveness

- 4.9 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of ranibizumab. It agreed that, of the 4 RCTs identified, it was appropriate to concentrate on the 2 larger, more directly relevant trials, RESTORE and DRCR.net. It noted that both trials were judged to be of high methodological quality by the manufacturer, and that the ERG agreed with this assessment. The Committee was aware that the studies were of relatively short duration, providing treatment for up to 3 years, and did not include long-term follow-up. The Committee concluded that the quality of the clinical-effectiveness evidence for ranibizumab was acceptable.
- 4.10 The Committee noted that, based on the results of the RESTORE study, ranibizumab (alone or in combination with laser photocoagulation) is associated with immediate and sustained gains in visual acuity in the treated eye, whereas improvement with laser photocoagulation alone is significantly less marked. The Committee understood from the clinical trial evidence that adding laser photocoagulation to ranibizumab does not appear to provide any additional improvement in vision over 2 years. However, it was aware of the clinical

specialists' belief that laser photocoagulation is more likely than ranibizumab to have long-term benefits, and that this could reduce the number of injections of ranibizumab needed after 2 years, although this cannot be confirmed using current evidence. The Committee concluded that, when compared with laser photocoagulation alone, treatment regimens that include ranibizumab are effective in improving visual acuity in the treated eye over 2 years, but that there is no evidence of additional benefit in adding laser photocoagulation to ranibizumab. The Committee was aware that this is inconsistent with the expectations of the clinical specialists.

- 4.11 The Committee noted that initial subgroup analyses in both RESTORE and DRCR.net had shown little evidence of differences in clinical effectiveness by subgroup. It understood from the manufacturer's evidence that, in RESTORE, gains in visual acuity associated with ranibizumab were greatest in participants with thicker retinas and more severe visual impairment at baseline. In particular, it noted the manufacturer's suggestion that ranibizumab could be expected to have a superior relative effect among people with thicker retinas (see [section 3.30](#)). The Committee was aware that the manufacturer had provided evidence in its rapid review submission to confirm this subgroup effect by testing for interaction between retinal thickness and treatment allocation. The Committee noted that the manufacturer's revised subgroup analyses according to retinal thickness relied on different categories of retinal thickness to those presented in NICE technology appraisal guidance 237 and also differed from those specified in the methods for subgroup analyses of the RESTORE study. The Committee also noted that changing these categories led to different results. However, the Committee acknowledged the clinical specialists' suggestion that laser photocoagulation would be less clinically effective in people with a thicker retina. Therefore, the Committee concluded that it had received sufficient evidence of biological plausibility for a clinically relevant subgroup in which ranibizumab has a significantly greater relative effect.
- 4.12 The Committee considered the generalisability of the results of the RESTORE study to people with diabetic macular oedema in clinical practice. The Committee heard from the clinical specialists that glycaemic control as reflected by HbA1c varies more in clinical practice than in trials, because the RESTORE trial excluded people with HbA1c values of 10% or more. The Committee also noted the comments on the use and effects of laser photocoagulation from the clinical

specialists (see section 4.10), and discussed whether the trials accurately reflect the way in which ranibizumab would be combined with laser therapy in clinical practice. The Committee concluded that the generalisability of trial results to the population with diabetic macular oedema seen in clinical practice is uncertain. The Committee also expressed concerns about whether the proportion of people who were treated in both eyes in the RESTORE study reflected clinical practice. The Committee concluded that the lack of evidence on vision in both eyes, as presented by the manufacturer in its original submission for NICE technology appraisal guidance 237, increased its uncertainty about how the effects of ranibizumab demonstrated in the trials would translate into benefits for people with diabetic macular oedema in clinical practice.

Cost effectiveness

- 4.13 The Committee discussed the appropriate approach for determining the cost effectiveness of ranibizumab. The Committee noted that the manufacturer's original base case and all additional original analyses performed by the manufacturer and the ERG suggest that combination therapy is more expensive and little or no more effective than ranibizumab alone. As a consequence, the Committee concluded that ranibizumab and laser photocoagulation as part of a simultaneous treatment strategy could not be recommended as an effective use of NHS resources. However, the Committee also heard from the clinical specialists that people currently treated with ranibizumab are likely to have had laser photocoagulation, which the clinical specialists believed is more likely to be associated with a long-term decrease in the recurrence of diabetic macular oedema than treatment with ranibizumab. The Committee agreed with the ERG's suggestion and consultation comments from retinal specialists that it is possible that ranibizumab and laser photocoagulation in a sequential treatment algorithm could provide a valuable treatment option. However, because no evidence to support this was available, the Committee concluded that it could not make separate recommendations on the sequential use of ranibizumab and laser photocoagulation.
- 4.14 When it reviewed the manufacturer's revised model submitted in NICE technology appraisal guidance 237, the Committee concluded that the model did not reflect likely clinical practice in at least 6 respects, as described in [section 3.46](#). The

manufacturer addressed these issues in its rapid review submission, and offered a revised patient access scheme (see [sections 3.47 to 3.49](#)).

- 4.15 The Committee discussed the manufacturer's approach to estimating the cost effectiveness of treating both eyes, in which it multiplied the ICERs generated in its better-seeing eye model by a factor of 1.5. The Committee was aware that this approach was consistent with that adopted by the Committee in [NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#) and that the same approach was used by the Committee when estimating the most plausible ICER in NICE technology appraisal guidance 237. The Committee also considered the new, alternative approach taken by the ERG in its 6 scenario analyses, which made explicit assumptions about the impact on costs and outcomes associated with treating only the worse-seeing eye, only the better-seeing eye or both eyes. The Committee noted that the ERG's 6 scenario analyses varied both the health-related quality of life impact of changes in the vision of the worse-seeing eye and the resultant QALYs associated with treatment of the worse-seeing eye or both eyes. The Committee agreed that, without available data on health-related quality of life associated with vision in both eyes, these scenarios fully explored the impact of treating both eyes on the relative cost effectiveness of ranibizumab. The Committee noted that, although there is little evidence of the impact of vision in the worse-seeing eye on health-related quality of life, the Brown study suggested that among people who had good vision in their better-seeing eye, the worse-seeing-eye contributed little to health-related quality of life. The Committee therefore considered scenario analysis 3 to be consistent with previous appraisals, which suggested that changes in vision for people treated in their worse-seeing eye had 30% of the health-related quality of life impact of the same change in vision from treating the better-seeing eye. In response to the rapid review appraisal consultation document, the Royal College of Ophthalmologists commented that the ERG's approach seemed logical, but that scenario 4 might be more appropriate. However, in the absence of new empirical evidence to suggest otherwise, the Committee accepted that scenario 3 reasonably reflected the clinical situation for people with diabetic macular oedema. The Committee concluded that the ERG's more comprehensive approach to modelling treatment of both eyes was likely to be more valid than multiplying the ICER associated with treating the better-seeing eye by 1.5 because it explored more explicitly the impact on costs and outcomes associated

with treating only 1 or both eyes.

4.16 The Committee considered the cost-effectiveness analyses presented by the manufacturer in its response to the appraisal consultation document for the rapid review of NICE technology appraisal guidance 237, which adopted the approach taken by the ERG (see [sections 3.58 to 3.60](#)). The Committee discussed the manufacturer's approach to estimating the proportion of people who would be treated in the better-seeing eye only, worse-seeing eye only or both eyes. The Committee noted that, as part of these 3 new analyses, the manufacturer presented data on the proportion of patients in RESTORE whom the manufacturer considered as having the same vision in both eyes at the start of treatment. The Committee was surprised that the manufacturer had not presented these data earlier in the appraisal. However, the Committee acknowledged that, although the manufacturer had originally proposed that patients would need treatment in only 1 eye despite bilateral disease, it had subsequently attempted to consider the cost effectiveness of treating both eyes in its rapid review submission. The Committee heard from the manufacturer that it considered the same-seeing eye pertinent only after the Committee had expressed its preference for the ERG's approach to estimating the costs and QALYs associated with treating both eyes. The Committee also heard from the manufacturer that it chose its definition of a same-seeing eye from a single study, that it was aware that other definitions existed, and that it had not taken a systematic approach to assessing other possible definitions. The Committee noted that the ICERs did not vary substantially between the 3 analyses presented by the manufacturer. The Committee concluded, given its concerns around the definition of same-seeing eyes, that analysis 2 (which suggested that the same-seeing eye has a visual acuity within 1 letter of the other eye) was the most plausible of the 3 new analyses presented by the manufacturer.

4.17 The Committee considered the utility values that quantified the changes in health-related quality of life attributed to vision in the manufacturer's new model in its rapid review submission. It was aware that the manufacturer used utility values estimated from the study by Czoski-Murray et al., in which members of the UK general public valued levels of visual impairment simulated by wearing vision-worsening contact lenses in both eyes. The Committee noted that this study resulted in a broader range of utility values between best and worst health states in the model than those used in the manufacturer's original submission in

NICE technology appraisal guidance 237, which were estimated from the RESTORE study and which the Committee considered to be unrealistically large (see [section 3.26](#)). The Committee also noted that participants in the Czoski-Murray study wore the lenses simulating bilateral visual impairment for a short period of time (between 1.5 and 2 hours). Therefore, the Committee considered that the participants may have overstated the detrimental impact on health-related quality of life of visual impairment in both eyes because they had little time to adjust to it. The Committee was aware that the Brown study identified by the ERG measured health-related quality of life directly from patients with impaired vision in at least 1 eye, and that this produced a narrower range of utility values than the study by Czoski-Murray et al. In consideration of a comment from the manufacturer who suggested that the utility values from the Brown study were not in line with the NICE reference case, the Committee noted that neither set of utility values was in line with the NICE reference case for measuring and valuing health effects. The Committee concluded that there was uncertainty about which utility data were most appropriate to include in the model. However, the Committee agreed that, in the absence of further evidence, it was reasonable to assume that the range of utility values would probably lie somewhere in between those estimated from the Czoski-Murray and Brown studies.

- 4.18 The Committee discussed the manufacturer's assumptions about how often people would receive ranibizumab in clinical practice. The Committee noted that, on the basis of the results from an extension to the RESTORE study available at the time of the rapid review submission, the manufacturer assumed that people would need 4 injections in year 2 and 3 injections in year 3 and no more injections from year 4 onwards. The Committee commented that it was unlikely that people who received 3 injections in year 3 would receive no further injections in year 4, especially if vision was assumed to remain stable during this period. The Committee was aware that some consultees had suggested that people with diabetic macular oedema would need more frequent treatment with ranibizumab than was assumed by the manufacturer. The Committee also noted that uncertainty remained about whether people would need ranibizumab beyond 4 years and, if they did, what the costs of ongoing treatment would be. However, the Committee acknowledged that the manufacturer had attempted to address this uncertainty by conducting a threshold analysis to assess the maximum number of injections per person that could be administered while maintaining an ICER below £30,000 per QALY gained. The Committee was aware that these

analyses allowed for only 4 additional injections in the first 3 years of the model. The Committee concluded that, without longer-term clinical data, significant uncertainty remained about the number of ranibizumab injections that people with diabetic macular oedema are likely to need.

- 4.19 The Committee considered the manufacturer's assumptions about how vision in the treated eye improved and deteriorated beyond the third year of the model, when the model assumes that ranibizumab treatment finishes. It understood that, although vision deteriorated over time in the model, it did so at the same rate in people previously treated with ranibizumab as in people who had previously been treated with laser photocoagulation. The Committee was aware of the opinion of clinical specialists that the most important effect of ranibizumab is to reduce the permeability of blood vessels and oedema in the eye, and heard from the clinical specialists that it is implausible that this effect would persist in the long term. By contrast, the benefits to vision from laser photocoagulation, although not as great as those of ranibizumab, are believed to last longer. The Committee noted that the manufacturer reduced uncertainty about the projected effects of ranibizumab treatment by following the approach discussed by the Committee in NICE technology appraisal guidance 237 and adopting a 10-year time horizon. The Committee also noted that this approach was consistent with previous appraisals. The Committee was aware of the new clinical evidence submitted by consultees in their response to the rapid review appraisal consultation document. The Committee understood that the consideration of such new clinical evidence on the long-term clinical benefits of the comparator treatment laser photocoagulation is beyond the remit of a rapid review, and would require a full review of the appraisal. Therefore the Committee concluded that, although significant uncertainty remains about the long-term benefit of ranibizumab treatment, compared with the manufacturer's original submission, the rapid review model more accurately reflects the duration of benefit that could be expected from treatment with ranibizumab.
- 4.20 The Committee considered the manufacturer's assumptions about the number of treatment and monitoring visits for people treated with ranibizumab and those treated with laser photocoagulation. The Committee was aware that in its original submission in NICE technology appraisal guidance 237, the manufacturer had assumed that a visit for treatment with ranibizumab would double as a monitoring visit and that people treated with laser photocoagulation would need a separate

monitoring visit. The Committee was unaware of any clinical evidence to justify this difference, and the manufacturer had not explained the difference in its original submission or in consultation comments. The Committee noted that the manufacturer had addressed this issue in its rapid review submission by assuming that a treatment visit for people receiving ranibizumab or laser photocoagulation doubles as a monitoring visit. The Committee concluded that, compared with the manufacturer's original submission, the rapid review model provided a more plausible reflection of the number of treatment and monitoring visits that people receiving ranibizumab treatment or laser photocoagulation would need.

- 4.21 The Committee considered whether the revised base-case model applies to the population with diabetic macular oedema in England and Wales. It noted the clinical specialists' advice that glycaemic control as reflected by HbA1c is likely to be worse in clinical practice than in the RESTORE trial, which excluded people with HbA1c levels of 10% or more (see section 4.12). The Committee observed that a subgroup analysis provided as part of the manufacturer's original submission for NICE technology appraisal guidance 237 suggested that restricting the analysis to people with good glycaemic control (HbA1c less than 8%) produced a much lower ICER than the ICER based on the group of people with poor control (HbA1c 8% or more; see [section 3.18](#)). The Committee noted that the manufacturer did not provide further analyses for these subgroups in its rapid review submission because of the relatively small sample sizes, which may have resulted in a small number of people in the extreme health states influencing the results. The Committee was aware of the new clinical evidence submitted by the manufacturer in response to the consultation on the rapid review appraisal consultation document. The Committee understood that submission of such further evidence would not normally be expected in the context of a rapid review, and accepted that this evidence could not be considered without formal review by the ERG. The Committee acknowledged that the issue of glycaemic control had been considered in NICE technology appraisal guidance 237, and that the Committee's considerations had been upheld at appeal. Based on the evidence provided in the manufacturer's original submission, the Committee agreed that uncertainty remained about the cost effectiveness of ranibizumab in people with poorer glycaemic control. Therefore, the Committee concluded that the manufacturer's model would probably generate a higher ICER if it was more reflective of the population seen in routine clinical practice.

4.22 The Committee discussed what could be considered as the most plausible ICERs. In the Committee's view, ICERs reflecting the possibility of treating both eyes were the most useful starting points for considering the cost effectiveness of ranibizumab for treating diabetic macular oedema. The Committee was aware that the manufacturer's rapid review base-case model produced an ICER of £21,200 per QALY gained for treating both eyes by multiplying the ICER for the better-seeing eye model by a factor of 1.5. The Committee agreed that this ICER was from a model that relied on a more plausible set of assumptions than those used in the manufacturer's original submission for NICE technology appraisal guidance 237. However, the Committee also acknowledged the ERG's technically more comprehensive approach of accounting for treatment in both eyes and noted that the manufacturer acknowledged the advantages of this approach. The Committee noted that this approach was subsequently adopted by the manufacturer in its response to the rapid review appraisal consultation document and led to ICERs in the range of £24,600 to £31,600 per QALY gained depending on the utility values used in the model for the Committee's preferred analysis. The Committee agreed that these ICERs would increase if the model accounted for people needing more than 4 treatments with ranibizumab beyond the third year, if people who had laser photocoagulation maintained any improvements in vision after treatment for longer than people treated with ranibizumab, and if the model better reflected the population with poorer glycaemic control seen in routine clinical practice. The Committee concluded that the most plausible ICER was likely to be above £30,000 per QALY gained, and that it therefore could not recommend ranibizumab as an effective use of NHS resources for the treatment of all people with diabetic macular oedema.

4.23 The Committee discussed whether it had received evidence of any groups of people for whom ranibizumab could be considered an effective use of NHS resources. It noted that, in its rapid review submission, the manufacturer provided additional subgroup analyses that showed that ranibizumab has a lower ICER in people with thicker retinas (central retinal thickness of 400 micrometres or more) than in people with thinner retinas (central retinal thickness of less than 400 micrometres) at the start of treatment. The Committee recognised the clinical plausibility of a greater relative efficacy of ranibizumab in people with a central retinal thickness of 400 micrometres or more, because it understood that laser photocoagulation may be less effective when used on a thicker retina. The Committee noted that the manufacturer had presented statistical evidence of

greater clinical effectiveness in this predefined group. The Committee also noted that the manufacturer had reduced the impact of small sample sizes, which had been raised as a concern in NICE technology appraisal guidance 237, by combining groups of people with thinner retinas (central retinal thickness less than 300 micrometres and 300 to 400 micrometres) into 1 larger group (people with central retinal thickness greater than 400 micrometres). This also produced more plausible cost-effectiveness results across the 2 groups. The Committee also acknowledged that the manufacturer had adequately accounted for differences in costs and outcomes for these subgroups by making adjustments to subgroup-specific parameters for other important model inputs. The Committee therefore concluded that the manufacturer had provided robust evidence demonstrating a subgroup effect in favour of people with thicker retinas.

4.24 The Committee considered the most plausible ICERs for people with thicker retinas (central retinal thickness of 400 micrometres or more) at the start of treatment. The Committee noted that the manufacturer's rapid review model produced an ICER of £13,300 per QALY gained for treating both eyes in this group by multiplying the ICER for the better-seeing eye model by a factor of 1.5. The Committee agreed that this ICER would increase if the model accounted for people needing more frequent treatment with ranibizumab beyond the third year, if people who had laser photocoagulation maintained any improvements in vision after treatment for longer than people who had ranibizumab, if the model better reflected the population with poorer glycaemic control seen in routine clinical practice, and if people with thicker retinas had higher rates of mortality than people with thinner retinas. The Committee also noted that neither the ERG nor the manufacturer provided exploratory scenario analyses for people with central retinal thickness of 400 micrometres or more. However, the Committee agreed that the ICER would likely increase if the ERG's approach of adapting the manufacturer's model to consider treating both eyes was used along with the Committee's preferred assumptions. The Committee therefore concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be higher than the manufacturer's estimate, but would be under £25,000 per QALY gained. The Committee also considered the manufacturer's suggestion in response to the rapid review appraisal consultation document that ranibizumab would be cost effective for the whole population. However, the Committee noted that the ICER for treating people with thinner retinas (central retinal thickness of less than 400 micrometres) was £43,300 per QALY gained in the manufacturer's

rapid review model and that ranibizumab would therefore not be an effective use of NHS resources in this group. Therefore the Committee recommended ranibizumab as an option for treating visual impairment due to diabetic macular oedema only if the eye has a central retinal thickness of 400 micrometres or more at the start of treatment.

- 4.25 The Committee noted that the scope for the appraisal included bevacizumab as a comparator. It was also aware of its previous conclusions on bevacizumab in NICE technology appraisal guidance 237, that ranibizumab at that time did not represent an effective use of NHS resources when compared with laser photocoagulation, and that therefore the Committee did not believe that considering evidence for bevacizumab would have altered its decision. However, because the Committee had concluded after the rapid review that ranibizumab represents a cost-effective use of NHS resources when compared with laser photocoagulation for people with a central retinal thickness of 400 micrometres or more, it discussed the comparison of ranibizumab with bevacizumab. The Committee noted and reviewed information from the regulatory authorities to prescribers in which the use of bevacizumab as an intravitreal injection in people with diabetic macular oedema is considered 'unlicensed'. Also, the Committee heard conflicting evidence about the extent to which bevacizumab is currently used to treat diabetic macular oedema in England and Wales. It concluded that bevacizumab is adopted by some clinicians and funded by some NHS trusts, but is not in use throughout the NHS. The Committee was aware that some consultees and commentators supported a comparison with bevacizumab and others opposed it. The Committee discussed whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible. The Committee recognised that a formal comparison of the 2 drugs would need evidence not only of all aspects of clinical effectiveness and safety, but also of the costs associated with preparing and administering bevacizumab, including the dose and number of injections needed. The Committee agreed that such evidence, in particular about the balance of harms and benefits associated with bevacizumab, was not readily available for people with diabetic macular oedema. The Committee also noted that it was unaware of any evidence of the effectiveness of intravitreal bevacizumab compared with ranibizumab in the subgroup of patients with thicker retinas. The Committee agreed that, taking into account all these uncertainties, it could not consider a comparison of ranibizumab with bevacizumab. The Committee also concluded that further

research directly comparing the clinical and cost effectiveness of ranibizumab and bevacizumab in people with diabetic macular oedema would reduce some of these uncertainties.

- 4.26 The Committee discussed whether ranibizumab should be considered an innovative treatment. It considered that, in terms of both pharmacological progress and potential benefits for people with diabetic macular oedema, the development of the anti-angiogenic drugs pegaptanib sodium and bevacizumab preceded that of ranibizumab. Therefore, the Committee concluded that ranibizumab itself could not properly be considered to provide distinctive pharmacological innovation. The Committee further noted that the analyses of the incremental health benefit of ranibizumab were based on a comparison with laser photocoagulation, and that the Committee had not been alerted to any benefits that were not already captured in the QALY measure. The Committee was also aware that, before NICE technology appraisal guidance 237 was published, the Committee's conclusions on innovation as described above were upheld by the Appeal Panel. It therefore concluded that the incremental value of ranibizumab for people with diabetic macular oedema had been appropriately captured.
- 4.27 The Committee discussed the proposed date for review of the guidance. The Committee was aware of the emerging evidence on the effectiveness and safety of bevacizumab as a treatment option for diabetic macular oedema, including work undertaken by NICE's Decision Support Unit and ongoing clinical trials comparing bevacizumab with ranibizumab in diabetic macular oedema and other eye diseases. The Committee was also aware that additional clinical data, including 3-year results from the DRCR.net study, had become available since the publication of NICE technology appraisal guidance 237, but that these data could not be considered as part of the rapid review process. The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015.
- 4.28 The Committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its preliminary recommendations in any way. During

the scoping phase of the appraisal, NICE had received evidence that some people in full-time residential care had restricted access to treatment for diabetic macular oedema. However, consultees suggested that the national screening programmes for diabetic retinopathy in England and Wales has reduced this inequality across the NHS. In submissions, the Committee had been made aware that there is a higher prevalence of diabetes in people of South Asian, African and African–Caribbean family origin and that, among people with diabetes, sight-threatening eye disease is more common in people of African and African–Caribbean family origin than in white Europeans. However, the Committee agreed that this was an issue that could not be addressed in a technology appraisal.

Summary of Appraisal Committee's key conclusions

Key conclusion (sections 1.1, 4.22, 4.24)

Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- the manufacturers of ranibizumab (branded or biosimilar) provide it at a discount level no lower than the discount agreed in the patient access scheme.

The Committee concluded that the most plausible ICER for the treatment of all people with diabetic macular oedema was likely to be above £30,000 per QALY gained, and that it therefore could not recommend ranibizumab as an effective use of NHS resources.

The Committee concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be under £25,000 per QALY gained. Therefore the Committee recommended ranibizumab as an option for treating diabetic macular oedema only for people with a central retinal thickness of 400 micrometres or more at the start of treatment.

Current practice

Clinical need of patients, including the availability of alternative treatments (sections 4.2, 4.3)

The Committee understood from patient experts that visual impairment has a substantial negative impact on quality of life and activities of daily living in people with diabetic macular oedema. The Committee heard from the clinical specialists that the current standard treatment for diabetic macular oedema is focal and/or grid laser photocoagulation.

The technology

Proposed benefits of the technology; how innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? (section 4.26)

The Committee considered that, in terms of both pharmacological progress and potential benefits for people with diabetic macular oedema, the development of the anti-angiogenic drugs pegaptanib sodium and bevacizumab preceded that of ranibizumab. Therefore, the Committee concluded that ranibizumab itself could not properly be considered to provide distinctive pharmacological innovation.

What is the position of the treatment in the pathway of care for the condition? (section 4.4)

The Committee heard from the clinical specialists that they would consider using ranibizumab either on its own or in a treatment strategy including laser photocoagulation given before, after or at the same time as ranibizumab.

Adverse reactions (section 4.8)

The Committee understood from the clinical specialists and patient experts that ranibizumab is generally well tolerated.

Evidence for clinical effectiveness

Availability, nature and quality of evidence (section 4.9)

The Committee agreed that, of the 4 RCTs identified, it was appropriate to concentrate on the 2 larger, more directly relevant trials, RESTORE and DRCR.net. It noted that both trials were judged to be of high methodological quality by the manufacturer, and that the ERG agreed with this assessment.

Relevance to general clinical practice in the NHS (section 4.12)

The Committee heard from the clinical specialists that glycaemic control as reflected by HbA1c varies more in clinical practice than in trials, because the RESTORE trial excluded people with HbA1c values of 10% or more. The Committee also noted the comments on the use and effects of laser photocoagulation from the clinical specialists, and discussed whether the trials accurately reflect the way in which ranibizumab would be combined with laser therapy in clinical practice. The Committee concluded that the generalisability of trial results to the population with diabetic macular oedema seen in clinical practice is uncertain.

Uncertainties generated by the evidence (sections 4.10, 4.12)

The Committee concluded that there is no evidence of additional benefit in adding laser photocoagulation to ranibizumab, but that this is inconsistent with the expectations of the clinical specialists.

The Committee concluded that the lack of evidence on vision in both eyes increased its uncertainty about how the effects of ranibizumab demonstrated in the trials would translate into benefits for people with diabetic macular oedema in clinical practice.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? (section 4.11)

The Committee understood from the manufacturer's evidence that, in RESTORE, gains in visual acuity associated with ranibizumab were greatest in participants with thicker retinas and more severe visual impairment at baseline. In particular, it noted the manufacturer's suggestion that ranibizumab could be expected to have a superior relative effect among people with thicker retinas. The Committee was aware that the manufacturer had provided

evidence in its rapid review submission to confirm this subgroup effect by testing for interaction between retinal thickness and treatment allocation. Therefore, the Committee concluded that it had received evidence of a clinically relevant subgroup in which ranibizumab has a significantly greater relative effect.

Estimate of the size of the clinical effectiveness including strength of supporting evidence (section 4.10)

The Committee concluded that, when compared with laser photocoagulation alone, treatment regimens that include ranibizumab are effective in improving visual acuity in the treated eye over 2 years, but that there is no evidence of additional benefit in adding laser photocoagulation to ranibizumab.

Evidence for cost effectiveness

Availability and nature of evidence (section 4.14)

When it reviewed the manufacturer's revised model submitted in NICE technology appraisal guidance 237, the Committee concluded that the model did not reflect likely clinical practice in at least 6 respects. The manufacturer addressed these issues in its rapid review submission, and offered a revised patient access scheme.

Uncertainties around and plausibility of assumptions and inputs in the economic model (section 4.22)

The Committee was aware that the manufacturer's base-case model produced an ICER of £21,200 per QALY gained for treating both eyes by multiplying the ICER for the better-seeing eye model by a factor of 1.5. The Committee agreed that this ICER was from a model that relied on a more plausible set of assumptions than those used in the manufacturer's original submission for NICE technology appraisal guidance 237. However, the Committee also acknowledged the ERG's technically more comprehensive approach of accounting for treatment in both eyes explored by the ERG and noted that the manufacturer acknowledged the advantages of this approach. The Committee noted that this approach was subsequently adopted by the manufacturer in its response to the rapid review appraisal consultation document and led to ICERs in the range of £24,600 to £31,600 per QALY gained depending on the utility values used in the model for the Committee's preferred analysis. The Committee agreed that these ICERs would increase if

the model accounted for people needing more than 4 treatments with ranibizumab beyond the third year, if people who had laser photocoagulation maintained any improvements in vision after treatment longer than people treated with ranibizumab, and if the model better reflected the population with poorer glycaemic control seen in routine clinical practice.

Incorporation of health-related quality-of-life benefits and utility values; have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? (section 4.17)

The Committee concluded that there was uncertainty about which utility data were most appropriate to include in the model. However, the Committee agreed that, in the absence of further evidence, it was reasonable to assume that the range of utility values would probably lie somewhere in between those estimated from the Czoski-Murray and Brown studies.

Are there specific groups of people for whom the technology is particularly cost effective? (sections 4.23, 4.24)

The Committee concluded that the manufacturer had provided robust evidence demonstrating a subgroup effect in favour of people with thicker retinas.

The Committee concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be higher than the manufacturer's estimate, but would be under £25,000 per QALY gained.

What are the key drivers of cost effectiveness? (sections 4.15 to 4.21)

The Committee concluded that the cost-effectiveness results were driven by the manufacturer's assumptions about: the need to treat both eyes of people with diabetic macular oedema, the utility associated with changes in vision of the treated eye, likely frequency of ranibizumab injections, the expected duration of benefit from ranibizumab treatment, the number of treatment visits and monitoring visits needed, and the generalisability of the economic evidence, especially about glycaemic control in the treated population.

Most likely cost-effectiveness estimate (given as an ICER; sections 4.22, 4.24)

The Committee concluded that the most plausible ICER for the treatment of all people with diabetic macular oedema was likely to be above £30,000 per QALY gained, and that it therefore could not recommend ranibizumab as an effective use of NHS resources.

The Committee concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be higher than the manufacturer's estimate, but would be under £25,000 per QALY gained.

Additional factors taken into account

Patient access schemes (PPRS) (section 2.4)

The manufacturer has agreed a patient access scheme with the Department of Health which makes ranibizumab available with a discount applied to all invoices. The size of the discount is commercial in confidence.

End-of-life considerations

Not applicable.

Equalities considerations and social value judgements (section 4.28)

NICE had received evidence that some people in full-time residential care had restricted access to treatment for diabetic macular oedema. However, consultees suggested that the national screening programme for diabetic retinopathy in England and Wales has reduced this inequality across the NHS. The Committee had been made aware that there is a higher prevalence of diabetes in people of South Asian, African and African–Caribbean family origin and that, among people with diabetes, sight-threatening eye disease is more common in people of African and African–Caribbean family origin than in white Europeans. However, the Committee agreed that this was an issue that could not be addressed in a technology appraisal.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has visual impairment due to diabetic macular oedema and the doctor responsible for their care thinks that ranibizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

- 6.1 The Committee concluded that further research directly comparing the clinical and cost effectiveness of ranibizumab and bevacizumab in people with diabetic macular oedema should be conducted.

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

DrAmandaAdler(Chair)

Consultant Physician, Addenbrooke's Hospital

ProfessorKenStein(ViceChair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

DrRayArmstrong

Consultant Rheumatologist, Southampton General Hospital

DrJeffAronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

DrPeterBarry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

DrMichaelBoscoe

Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation

Trust

ProfessorJohnCairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

DrMarkChakravarty

External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

MarkChapman

Health Economics and Market Access Manager, Medtronic UK

ProfessorFergusGleeson

Consultant Radiologist, Churchill Hospital, Oxford

EleanorGrey

Lay member

ProfessorDanielHochhauser

Consultant in Medical Oncology

DrNeillosson

General Practitioner

AnneJoshua

Associate Director of Pharmacy, NHS Direct

TerenceLewis

Lay member

ProfessorRuairidhMilne

Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

DrRubinMinhas

General Practitioner and Clinical Director, BMJ Evidence Centre

DrElizabethMurray

Reader in Primary Care, University College London

DrPeterNorrie

Principal Lecturer in Nursing, DeMontfort University

ProfessorStephenPalmer

Professor of Health Economics, Centre for Health Economics, University of York

DrSanjeevPatel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

DrJohnPounsford

Consultant Physician, Frenchay Hospital, Bristol

DrDaniellePreedy

Lay member

DrCaseyQuinn

Lecturer in Health Economics, Division of Primary Care, University of Nottingham

DrJohnRodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

AlunRoebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

DrFlorianAlexanderRuths

Consultant Psychiatrist and Cognitive Therapist at the Maudsley Hospital, London

NavinSewak

Primary Care Pharmacist, NHS Hammersmith and Fulham

RoderickSmith

Finance Director, West Kent Primary Care Trust

CliffSnelling

Lay member

MartaSoares

Research Fellow, Centre for Health Economics, University of York

ProfessorAndrewStevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

ProfessorRodTaylor

Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

DrColinWatts

Consultant Neurosurgeon, Addenbrooke's Hospital

TomWilson

Director of Contracting & Performance, NHS Tameside & Glossop

DrNerysWoolacott

Senior Research Fellow, Centre for Health Economics, University of York

B NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

GabrielRogers and MatthewDyer

Technical Leads

HelenKnight and DrKayNolan

Technical Advisers

JeremyPowell

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen Health Technology Assessment Group:

- Royle P, Cummins E, Henderson R et al. Ranibizumab for the treatment of diabetic macular oedema: a single technology appraisal. Aberdeen HTA Group 2011

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document. Organisations listed in 1 were also invited to make written submissions. Organisations listed in 2 and 3 had the opportunity to give their expert views. Organisations listed in 1 and 2 also have the opportunity to appeal against the final appraisal determination.

1 Manufacturer or sponsor:

- Novartis

2 Professional or specialist and patient or carer groups:

- Diabetes UK
- Macular Disease Society
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal College of Physicians
- Royal National Institute of Blind People (RNIB)

3 Other consultees:

- Department of Health
- Bridgend LHB

- Welsh Assembly Government

4 Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Roche Products

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on ranibizumab by attending the initial Committee discussion for NICE technology appraisal 237 and providing written evidence to the Committee. They were also invited to comment on the appraisal consultation document.

- Claire Bailey, nominated by the Royal National Institute of Blind People – clinical specialist
- Professor Yit Yang, nominated by the Royal College of Ophthalmologists – clinical specialist
- Jennifer Nosek, nominated by the Royal College of Nursing – clinical specialist
- Barbara McLaughlan, nominated by Royal National Institute of Blind People – patient expert
- Michael Stroud, nominated by Royal National Institute of Blind People – patient expert

D Representatives from the following manufacturer or sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis

Update information

January 2014: minor maintenance.

April 2013: The wording of the recommendation describing the patient access scheme (see section 1.1) has been amended to make it clear which scheme is being referred to.

October 2023: The wording of the recommendation describing the patient access scheme (see section 1.1) and section 2.4 have been updated to include procurement information about ranibizumab biosimilars.

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Accreditation

