NICE National Institute for Health and Care Excellence

NICE guidance

Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion

Technology appraisal guidance
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1 Recommendations

1.1 Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:

- following central retinal vein occlusion or
- following branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage and
- only if 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 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.

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2 The technology

2.1 Ranibizumab (Lucentis, Novartis) belongs to a class of drugs that block the action of vascular endothelial growth factor (VEGF)-A. Retinal vein occlusion (RVO) is a common cause of reduced vision as a result of retinal vascular disease. Thrombosis in the retinal veins causes an increase in retinal capillary pressure, resulting in increased capillary permeability and the discharge of blood and plasma into the retina. This leads to macular oedema and varying levels of ischaemia through reduced perfusion of capillaries. These changes trigger an increase in VEGF, which increases vascular permeability and new vessel proliferation. By inhibiting the action of VEGF-A, ranibizumab reduces oedema and limits visual loss or improves vision. Ranibizumab has a UK marketing authorisation for 'the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)'.

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 should be resumed if monitoring indicates a loss of visual acuity caused by macular oedema secondary to RVO, and continued until visual acuity has remained stable for 3 consecutive months. The interval between doses should not be shorter than 1 month. If there is no improvement in visual acuity over the course of the first 3 injections, continued treatment is not recommended.

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 to 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 commonly reported. For full details of adverse reactions and contraindications, see the summary of product characteristics.

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2.4 The manufacturer of branded ranibizumab (Lucentis, Novartis) has agreed a patient access scheme with the Department of Health, revised in the context of NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema, which makes ranibizumab available with a discount applied to all invoices. The level 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 technology by NICE 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 PAS.

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3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of ranibizumab and a review of this submission by the Evidence Review Group (ERG).

3.1 The manufacturer submitted evidence of clinical and cost effectiveness for ranibizumab compared with grid laser photocoagulation in people with visual impairment caused by macular oedema secondary to branch retinal vein occlusion (BRVO) and for ranibizumab compared with best supportive care in people with visual impairment caused by macular oedema secondary to central retinal vein occlusion (CRVO). The manufacturer stated that there was no direct or indirect evidence comparing the clinical effectiveness of ranibizumab with bevacizumab or dexamethasone intravitreal implant (which were defined as comparators in the scope for the appraisal). However, a comparison of the cost effectiveness of ranibizumab with dexamethasone intravitreal implant was included in the manufacturer's submission; this was not the case for bevacizumab (see sections 3.9 and 3.10).

3.2 The main sources of evidence presented in the manufacturer's submission came from the BRAVO and CRUISE randomised controlled trials (RCTs). These evaluated the efficacy of ranibizumab, compared with a sham procedure, for treating visual impairment caused by macular oedema secondary to BRVO and to CRVO respectively. The BRAVO (n=397) and CRUISE (n=392) trials were both 3-armed RCTs carried out at multiple centres in the USA. Patients were randomised equally to sham injection, monthly intraocular ranibizumab 0.3 mg or monthly intraocular ranibizumab 0.5 mg. Both trials included people with visual impairment caused by macular oedema who had been diagnosed in the 12 months before study initiation. Patients entered a 6-month treatment phase during which monthly injections were given, beginning on day 0. In the treatment phase of BRAVO, patients in both the sham injection and ranibizumab groups could receive grid laser photocoagulation for rescue treatment from 3 months. In both BRAVO and CRUISE, the treatment phase was followed by a 6-month observation phase during which all groups (that is, the sham group and the 2 ranibizumab groups) could receive ranibizumab as needed. Patients in the observation phase of BRAVO (but not CRUISE) could receive grid laser photocoagulation for rescue treatment from 3 months (that is, at month 9 of the

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study). The final treatment in both BRAVO and CRUISE was given at month 11, with a final study visit at month 12. Patients who completed the 12-month BRAVO and CRUISE trials could enter an open-label extension study (HORIZON).

3.3 The primary outcome in both BRAVO and CRUISE was the mean change from baseline in best corrected visual acuity (BCVA) score in the study eye at 6 months. BCVA score was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart, in which a score of 85 letters corresponds to normal visual acuity ('20/20 vision'). Secondary outcomes reported in both BRAVO and CRUISE included mean change from baseline in BCVA score over time up to 6 and 12 months, and the proportion of patients gaining or losing more than 15 letters in BCVA score at 6 and 12 months compared with baseline. The trials also reported results for several exploratory outcomes, including the mean change from baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) composite score up to 6 months. The NEI VFQ-25 has 25 questions that are designed to measure the effect of visual impairment on daily functioning and quality of life.

3.4 This appraisal considered the 0.5 mg dose of ranibizumab, which is the only dose with a UK marketing authorisation. In BRAVO, 91.7% of patients in the sham group and 95.4% in the ranibizumab group were treated in the 'worse-seeing eye' (that is, the eye affected by RVO). In CRUISE, 90.0% of patients in the sham group and 92.3% in the ranibizumab group were treated in their 'worse-seeing eye'. The mean number of ranibizumab injections in the treatment phase was 5.7 (BRAVO) and 5.6 (CRUISE). The average number of ranibizumab injections in the observation phase was 2.7 (BRAVO) and 3.3 (CRUISE). More than 80% of patients from the sham injection group in both BRAVO and CRUISE received ranibizumab as needed during the observation phase. During the first 6 months of the BRAVO trial, grid laser photocoagulation was used in 57.6% of patients in the sham injection group and in 21.4% of the patients in the ranibizumab group. Over the 12-month study period in BRAVO, 61.4% of patients in the sham (plus ranibizumab) group and 34.4% of patients in the ranibizumab group received rescue treatment with grid laser photocoagulation.

3.5 In BRAVO, at month 6, patients in the ranibizumab group had gained an average of 18.3 letters (95% confidence interval [CI] 16.0 to 20.6) from baseline BCVA score. This gain was statistically significant compared with the gain of 7.3 letters

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(95% CI 5.1 to 9.5) in the group receiving sham injection (p<0.0001). At month 12 of the BRAVO trial (that is, at the end of the 6-month observation period, during which all patients could receive ranibizumab as needed), the 0.5 mg ranibizumab group reported an average gain in BCVA baseline score of 18.3 letters (95% CI 15.8 to 20.9) compared with the sham (plus ranibizumab) group, which had gained 12.1 letters (95% CI 9.6 to 14.6, p<0.01). The observed improvement at month 6 from baseline in the NEI VFQ-25 composite score was statistically significantly greater in patients receiving ranibizumab (10.4 points, 95% CI 8.3 to 12.4) than in patients receiving sham injection (5.4 points, 95% CI 3.6 to 7.3; p<0.005). The manufacturer reported that overall the BRAVO trial showed a clinically meaningful and statistically significant effect of ranibizumab on visual acuity and patient-reported outcomes based on the NEI VFQ-25 at 6 months. The manufacturer carried out a post-hoc analysis stratified by rescue treatment with grid laser photocoagulation to investigate the effects of adding this treatment to ranibizumab. The manufacturer concluded that treating patients with grid laser photocoagulation as well as ranibizumab did not lead to the efficacy of ranibizumab being overestimated.

3.6 At month 6 in the CRUISE trial, patients in the ranibizumab group achieved a statistically significant mean gain in BCVA score from baseline of 14.9 letters (95% CI 12.6 to 17.2) compared with the sham group, who gained 0.8 letters (95% CI -2.0 to 3.6, p<0.0001). The manufacturer reported that the improvements in BCVA in the ranibizumab group at month 6 were generally maintained through to month 12 with treatment as needed (13.9 letters [95% CI 11.5 to 16.4] for ranibizumab; 7.3 letters [95% CI 4.5 to 10.0] for sham [plus ranibizumab] group; p<0.001). Patients receiving ranibizumab 0.5 mg showed statistically significantly greater improvements in patient-reported outcomes as measured by the NEI VFQ-25 (6.2 points, 95% CI 4.3 to 8.0) than patients receiving sham injection (2.8 points, 95% CI 0.8 to 4.7; p<0.05).

3.7 For patients who entered the open-label extension study (HORIZON), ranibizumab 0.5 mg was given at intervals of at least 30 days. Sixty-seven per cent of patients from BRAVO and 60% of patients from CRUISE completed month 12 of HORIZON. The primary outcome for the HORIZON extension study was mean change from HORIZON baseline in BCVA score up to 24 months. The manufacturer presented results from the first 12 months. From the BRAVO trial baseline, patients receiving sham (plus ranibizumab) and those receiving 0.5 mg

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ranibizumab had mean gains in BCVA score of 15.6 letters and 17.5 letters respectively. From the CRUISE trial baseline, patients receiving sham (plus ranibizumab) and those receiving 0.5 mg ranibizumab had mean gains in BCVA score of 7.6 and 12.0 letters respectively (no confidence intervals reported).

3.8 Adverse events were reported at 6 months and 12 months in both BRAVO and CRUISE trials, and for a further 12 months' follow-up in the HORIZON extension study. In BRAVO, at 6 months there were 7 ocular adverse events (5.4%) in the ranibizumab group compared with 17 (13%) in the sham group, excluding occurrences of raised intraocular pressure. Non-ocular serious adverse events (potentially related to vascular endothelial growth factor [VEGF] inhibition) at 6 months were higher in the ranibizumab group (5 events [3.8%]) than in the sham group (1 event [0.8%]). In CRUISE, at 6 months there were 13 ocular adverse events (10.1%) in the ranibizumab group compared with 25 (19.4%) in the sham group, excluding occurrences of raised intraocular pressure. In CRUISE, non-ocular serious adverse events (potentially related to VEGF inhibition) were similar in both the ranibizumab and sham groups (3 [2.3%] and 2 [1.6%] respectively). The most common adverse event reported in BRAVO and CRUISE at 12 months was cataract, with 8 (6.2%) and 9 (7%) instances associated with ranibizumab treatment respectively; in the sham (plus ranibizumab) group, 3 (2.6%) and 2 (1.8%) instances of cataract were reported for the treatment period of 6 to 12 months. Instances of raised intraocular pressure were reported in both BRAVO and CRUISE at 6 months but were academic in confidence, and therefore not reported here. In the HORIZON extension study, the incidence of any adverse event in the sham (plus ranibizumab) and ranibizumab groups was 2.2% and 5.8% respectively for the patients (with BRVO) recruited from BRAVO, 5.2% and 3% respectively for the patients (with CRVO) recruited from CRUISE.

3.9 A systematic review was undertaken to identify RCTs involving potential comparators for ranibizumab in the treatment of visual impairment caused by macular oedema secondary to RVO. The manufacturer discussed the feasibility of conducting a formal indirect comparison of ranibizumab with dexamethasone intravitreal implant or bevacizumab in CRVO, and an indirect comparison of ranibizumab with dexamethasone intravitreal implant, bevacizumab or grid laser photocoagulation in BRVO. For a comparison of ranibizumab and bevacizumab in CRVO, the manufacturer identified a study by Faghihi et al. (2008) but stated that there was not enough information about the baseline characteristics of patients

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in the study. For a comparison with bevacizumab in BRVO, studies by Moradian et al. (2011) and Russo et al. (2009) were identified. The manufacturer stated that an indirect comparison could not be conducted without bias because the length of time since diagnosis of macular oedema differed in Moradian et al. (2011) and BRAVO, and because the trial duration was different in all 3 studies. The manufacturer also considered that bevacizumab was not an appropriate comparator because it did not consider that its use in the NHS was routine or best practice. The manufacturer stated that an indirect comparison of ranibizumab and dexamethasone intravitreal implant could not be undertaken for CRVO or BRVO because of the population differences in trials involving these 2 treatments: patients had different lengths of time since diagnosis of macular oedema, different baseline ranges of BCVA and different retinal thickness in the BRAVO and CRUISE trials compared with the GENEVA studies (which compared dexamethasone with sham injection). The manufacturer also stated that ranibizumab could not be compared indirectly with grid laser photocoagulation because of fundamental differences in trial design between BRAVO, which was sham-injection-controlled, and the laser studies BVOS (1984) and Battaglia et al. (1999), which were not.

3.10 Although no formal indirect comparison of ranibizumab with other drug treatments was performed, the relative systemic safety profiles of ranibizumab and bevacizumab were discussed in the manufacturer's submission. The manufacturer stated that ranibizumab was associated with a better safety profile than bevacizumab. The manufacturer provided data from 3 large retrospective studies by Carneiro et al. (2011), Curtis et al. (2010) and Gower et al. (2011) in support of this statement, but these studies compared bevacizumab with ranibizumab for the treatment of age-related macular degeneration (AMD) rather than RVO. The manufacturer acknowledged that AMD manifests later in life than RVO, and so the average age of patients in the BRAVO and CRUISE trials was lower than in the studies of AMD.

3.11 For evidence of cost effectiveness, the manufacturer submitted a Markov state transition model comparing treatment with ranibizumab with grid laser photocoagulation (standard care) for visual impairment caused by macular oedema secondary to BRVO and with best supportive care for CRVO. Treatment was modelled over a 15-year time horizon for a hypothetical cohort of 1,000 patients with visual impairment because of macular oedema secondary to

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RVO, with a starting age of around 66 years. Eight BCVA health states and death are included in the model structure, with each health state having an associated utility and mortality risk depending on whether the 'better-seeing eye' or 'worse-seeing eye' is treated. In the manufacturer's base-case analysis, it was assumed that all patients are treated in their 'better-seeing eye'. People move through the model in monthly cycles, accumulating the utility associated with each health state they enter, together with the costs of treatment and subsequent monitoring. Additional costs and disutility associated with blindness were applied for people with a visual acuity equal to or less than 35 letters in the 'better-seeing eye'. The model assumed that a person's risk of mortality would increase with worsening visual acuity in the 'better-seeing eye'. A published study by Christ et al. (2008) was used to provide the risk levels by ETDRS bands. The manufacturer asserted that mortality associated with RVO would not be expected to result in any additional risk of mortality over and above that of the general population and as a consequence, the model did not include an assumption of excess mortality associated with RVO.

3.12 Transition probabilities were determined monthly and subsequently used to calculate overall monthly transition probabilities for months 0 to 1, months 2 to 6 and months 7 to 12. For CRVO, the probabilities derived from the sham group of the CRUISE trial for months 2 to 6 were applied to months 2 to 6, 7 to 12 and 13 to 24 in the best supportive care arm of the model. The manufacturer stated that this was because there were no comparative data beyond month 6; from this point in the trial treatment with ranibizumab could be given to people in either arm as needed. Similarly for BRVO, no comparative data existed beyond month 6. However, this was further complicated by the use of grid laser photocoagulation as a rescue treatment in both arms of the trial beyond month 3. Therefore the probabilities for months 7 to 12 were pooled from the sham and ranibizumab groups of BRAVO and applied to months 7 to 12 and months 13 to 24 in both arms of the model. Dexamethasone intravitreal implant was incorporated into the model by a combination of applying relative risks from 2 trials (GENEVA studies) and assigning probabilities observed in the control groups of the BRAVO and CRUISE trials.

3.13 The manufacturer conducted a systematic review of the literature to identify utility values for populations with visual impairment because of RVO, with priority given to populations with macular oedema secondary to BRVO or CRVO. From the

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results of this review, the manufacturer chose a study by Brown (1999) as the source of utilities for the model, stating that this was the only relevant study that reported utility values related to visual acuity. This is a US study assessing preferences for different levels of visual acuity in patients with vision loss from various causes, 7% of whom had RVO. The manufacturer's model applies different utility values to each BCVA health state, depending on whether the 'better-seeing eye' or 'worse-seeing eye' is treated. Although separate utility values for visual acuity in the 'better-seeing eye' and 'worse-seeing eye' were available from the study by Brown, the manufacturer stated that there was little difference between the worst and best health states for people treated in their 'worse-seeing eye' and therefore assumed a value of 0.85 for all BCVA health states for people treated in the 'worse-seeing eye' (that is, no gain from treatment). In addition, the base-case model assumed all people would be treated in their best-seeing eye and therefore this issue of utility gain for people treated in their 'worse-seeing eye' was not relevant to the base case. For people treated in their 'best-seeing eye' the maximum utility gain from treatment was 0.41 (that is, the difference between the best visual health state of 0.92 and the worst visual health state of 0.51). Utilities were not adjusted for age.

3.14 Costs included intervention and comparator costs, administration costs and follow-up visits. Grid laser photocoagulation (BRVO only) was assumed to incur no cost but an administration cost as an outpatient procedure was applied. The ranibizumab injection administration visit was costed as an office-based outpatient procedure, whereas the dexamethasone intravitreal implant injection was based on a weighted average of the cost of an outpatient procedure (25%) and day case procedure (75%) to account for its greater complexity. For ranibizumab, the frequency of injections was taken from the BRAVO and CRUISE trials. In addition, patients experiencing adverse events had an associated cost applied, and patients considered to be blind had the additional costs associated with blindness.

3.15 All of the manufacturer's base-case incremental cost-effectiveness ratios (ICERs) that were presented included an approved patient access scheme, which was offered by the manufacturer at the time of submission (and which was subsequently superseded). In the base case for BRVO, the ICER for ranibizumab compared with grid laser photocoagulation was £20,494 per quality-adjusted life year (QALY) gained. In the base case for CRVO, the ICER for ranibizumab

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compared with best supportive care was £8,643 per QALY gained. The base-case ICERs for ranibizumab compared with dexamethasone for BRVO and CRVO were £5,486 and £7,174 per QALY gained respectively. Incremental costs and QALYs for the base-case results were commercial in confidence and therefore cannot be presented here.

3.16 The manufacturer performed a deterministic sensitivity analysis and found the model to be sensitive to the frequency of injections and follow-up visits. The manufacturer performed scenario analyses to assess the impact of varying the proportion of people treated in their 'worse-seeing eye' and commented that this was a key driver of cost effectiveness. The manufacturer also presented probabilistic sensitivity analyses and concluded that the probability that ranibizumab was cost effective when compared with grid laser photocoagulation in BRVO was 45.5% and 57.2% at thresholds of £20,000 and £30,000 per QALY gained respectively. For ranibizumab compared with best supportive care in CRVO, the probability of cost effectiveness was estimated by the manufacturer to be 74.5% and 83.3% at thresholds of £20,000 and £30,000 per QALY gained respectively.

Evidence Review Group comments on the manufacturer's submission

3.17 The ERG noted that most patients with retinal ischaemia were excluded from the BRAVO and CRUISE trials, because one of the exclusion criteria was brisk afferent pupillary defect, which, as the manufacturer stated, equates to severe retinal ischaemia. Therefore, the ERG considered that the results of any analyses could only be applied to people without retinal ischaemia.

3.18 The ERG considered that the concomitant use of grid laser photocoagulation from month 3 confounded the results of the BRAVO study and that definite conclusions could not be drawn about the effects of ranibizumab compared with sham injection or grid laser photocoagulation alone. The ERG noted that there was not enough evidence to conclude that grid laser photocoagulation had no effect in the ranibizumab group. It also noted that the treatment period of the BRAVO trial was not long enough to capture any benefits of grid laser

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photocoagulation on patient outcomes, which may last longer than 3 years. Furthermore, clinical advice to the ERG suggested that ranibizumab and grid laser photocoagulation would not be used together to treat patients in clinical practice.

3.19 The ERG noted that from month 6 onwards people were allowed to have ranibizumab as needed and therefore considered the data up to month 6 to be the most relevant data for determining the comparative effectiveness of ranibizumab in treating visual impairment caused by macular oedema secondary to RVO. However, the ERG noted that this period may not be long enough to determine the long-term effects of ranibizumab.

3.20 The ERG questioned the manufacturer's view that an indirect estimate of the efficacy of ranibizumab compared with bevacizumab, dexamethasone and grid laser photocoagulation (for BRVO only) was not possible. Although the ERG accepted that there were differences in baseline characteristics between patients in the CRUISE, BRAVO and GENEVA trials (see section 3.9), it stated that this would not prevent an indirect comparison between ranibizumab and dexamethasone, and would likely favour ranibizumab. This was because at baseline the mean duration of macular oedema secondary to CRVO was 3 months in CRUISE and 5 months in GENEVA, and a greater mean duration of RVO tends to result in a poorer response to treatment. The ERG suggested that the impact of any bias could have been explored through critical assessment. The ERG agreed with the manufacturer that it was not possible to incorporate bevacizumab for people with CRVO into an adjusted indirect comparison because only 1 study of bevacizumab for CRVO had been identified in the manufacturer's submission (Faghihi et al. 2008), and this did not adequately report baseline characteristics. For BRVO, the ERG considered that studies of bevacizumab reported in the manufacturer's submission (see section 3.9) were suitable for inclusion in an indirect comparison with the first 3 months of data from BRAVO (that is, before rescue treatment with grid laser photocoagulation was permitted). Again, the ERG accepted that there would be some bias in this comparison, but overall the biases would likely favour ranibizumab because the duration of macular oedema in BRAVO was longer than in the study by Moradian et al. and because the Moradian study included more patients with ischaemia than BRAVO. The ERG highlighted that this could be explored in critical assessment.

3.21 From the trials reported in the manufacturer's submission, the ERG was able to

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construct a linear network of trials using BRAVO (ranibizumab compared with sham), Moradian et al. 2011 (bevacizumab compared with sham) and Russo et al. 2009 (bevacizumab compared with grid laser photocoagulation). The ERG commented that although the results should be treated with caution because they are exploratory, they estimated an approximately 3-letter improvement in visual acuity with ranibizumab over bevacizumab and an 8-letter improvement with ranibizumab over grid laser photocoagulation at month 3. However, the ERG did not consider the difference between bevacizumab and ranibizumab to be clinically meaningful from this analysis.

3.22 The ERG noted that in the base-case analysis the model assumed all patients were treated in the 'better-seeing eye', despite the fact that over 90% of patients in the BRAVO and CRUISE trials were treated in their 'worse-seeing eye'. The ERG considered that it was not reasonable to assume equivalent gains in utility and reductions in costs when treating a patient in their 'worse-seeing eye'. The ERG considered the manufacturer's use of a 'better-seeing eye' model to be inappropriate because RVO is predominantly a unilateral condition, and therefore most patients would receive treatment in their 'worse-seeing eye' only.

3.23 The ERG considered the pooled transition probabilities for ranibizumab, which the manufacturer stated had been necessary to account for the effect of grid laser photocoagulation in people with BRVO. The ERG commented that pooling would lead to an overestimate of the efficacy of ranibizumab because the benefit seen in patients in the sham group who received ranibizumab after the first 6 months would be added to the continued effect of ranibizumab in those patients initially randomised to receive ranibizumab. The ERG conducted sensitivity analyses using unpooled transition probabilities. It noted that the ICER for ranibizumab compared with grid laser photocoagulation (for BRVO) with this change alone increased the manufacturer's original base-case from £20,494 to £52,004 per QALY gained for months 7 to 12, and ranibizumab was dominated (was less clinically effective and more expensive) for months 13 to 24, and months 7 to 12 plus months 13 to 24 together. Incremental costs and QALYs for the base-case results were commercial in confidence and therefore cannot be presented here.

3.24 The ERG considered the manufacturer's exploratory economic analysis that incorporated dexamethasone intravitreal implant. The ERG commented that there was a potential bias towards ranibizumab in the manufacturer's approach (see

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section 3.20). The ERG conducted an exploratory indirect comparison of ranibizumab with dexamethasone intravitreal implant, which provided relative risks of an improvement in visual acuity of 10 letters (2 lines) or more for patients with macular oedema secondary to BRVO and CRVO (a relative risk of less than 1 favours ranibizumab). The relative risks increased from 0.55 to 0.79 for ranibizumab compared with dexamethasone in BRVO. For CRVO, the corresponding figures were 0.30 to 0.40. The ERG commented that the relative risks calculated from the manufacturer's model were more favourable to ranibizumab in both BRVO and CRVO. Moreover, because the ERG's indirect comparison was known to be biased towards ranibizumab, the manufacturer's approach to modelling dexamethasone was largely biased towards ranibizumab. However, the ERG commented that these results were exploratory and should therefore be interpreted with caution.

3.25 The ERG noted the manufacturer's assumption in the economic model that there is no mortality risk attributable to RVO. The ERG identified a UK-based study (Tsaloumas et al. 2000) that concluded that patients with RVO were at a significantly greater risk of death from myocardial infarction than the general population. The ERG was of the opinion that it would have been appropriate to include the relative risk of 1.6 reported by Tsaloumas in the manufacturer's base-case analysis.

3.26 The ERG noted the manufacturer had applied a mortality risk associated with the visual acuity level in the patient's 'better-seeing eye' using data from Christ et al. (2008). The ERG noted that this mortality risk would only apply to patients being treated in their 'better-seeing eye'. The ERG commented that if the model was amended to treat those with visual impairment in their 'worse-seeing eye' it would be appropriate to use a mortality risk associated with 'some' visual impairment in these patients.

3.27 The ERG noted that the utility values for visual acuity in the 'better-seeing eye' were taken from Brown (1999) rather than Czoski-Murray et al. (2009), an earlier version of which had been used (referred to as Brazier et al. 2006) in NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration. The ERG noted that the manufacturer's model assumes utilities are independent of age, although age adjustment is expected to have minimal impact on the ICERs. However, the ERG commented

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that age adjustment of the utilities presented by Czoski-Murray et al. (2009) was not necessary because age had already been adjusted for. The ERG commented that the study by Czoski-Murray et al. (2009) should therefore be used as the source for utility associated with visual acuity in the 'better-seeing eye' in this assessment. For the 'worse-seeing eye' the ERG was of the opinion that the available evidence from the Brown publication (which reported utilities by worse- and better-seeing eyes) suggested the maximum gain from treating a person's 'worse-seeing eye' would be 0.1.

3.28 The ERG carried out exploratory analyses varying several parameters. Assuming that only 10% (and not 100%) of people are treated in their 'better-seeing eye', applying utilities derived from Czoski-Murray et al. (2009), a 0.1 overall benefit associated with treating the 'worse-seeing eye' and an increased risk of mortality associated with RVO, the ICERs for ranibizumab compared with best supportive care and with dexamethasone in CRVO were £43,760 and £37,443 per QALY gained respectively. This formed the ERG's base-case estimate for CRVO. The ERG did not present further economic evaluation of ranibizumab compared with grid laser photocoagulation because it considered that the confounded data from BRAVO (in which grid laser photocoagulation was permitted in the ranibizumab arm after 3 months of treatment) was insufficient to inform an indirect comparison and be used in the economic model. When the ERG applied their preferred assumptions as above for ranibizumab compared with dexamethasone intravitreal implant in BRVO, this increased the manufacturer's base-case ICER from £5,486 to £31,122 per QALY gained. The ERG's exploratory analyses highlighted that the key drivers that increased the manufacturer's base-case ICERs were amending the proportion of patients treated in their 'better-seeing eye' (10% instead of 100%) and the assumption of some benefit associated with treating the 'worse-seeing eye'.

3.29 The ERG commented that its comparisons of ranibizumab with dexamethasone intravitreal implant for both BRVO and CRVO used relative risks derived from the manufacturer's model (0.55 for BRVO and 0.30 for CRVO) rather than those derived from the ERG's indirect comparison (0.79 and 0.40 respectively). The ERG commented that this would bias the results in favour of ranibizumab and if the ERG's suggested relative risks were applied, the ICER would increase further. The ERG also commented that the efficacy of dexamethasone was potentially underestimated because of differing patient characteristics in the trials that

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informed the comparison (patients had differing durations of macular oedema from diagnosis in the GENEVA trials compared with BRAVO and CRUISE). Therefore, the manufacturer's base-case ICERs may be underestimates. The ERG also highlighted that the ICER generated for ranibizumab compared with dexamethasone from the BRAVO trial is derived using the pooled transition probabilities in the original submission. Using the unpooled transition probabilities would increase the ICER further.

3.30 The ERG conducted an exploratory cost-minimisation analysis for ranibizumab compared with bevacizumab, assuming equivalent efficacy for the 2 treatments (in BRVO and CRVO) and an acquisition cost of £50 per month for bevacizumab. The ERG presented data on the incremental costs of ranibizumab compared with bevacizumab that included commercial-in-confidence information and so cannot be presented here. The ERG's analysis using the manufacturer's model suggested that ranibizumab would need to generate 1.5 times more QALYs than bevacizumab (each month between months 2 and 6) in macular oedema secondary to BRVO (without considering the revised patient access scheme implemented in NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema) to give an ICER at the top end of the range usually considered cost effective. Ranibizumab would need to generate 1.7 times more QALYs than bevacizumab for macular oedema secondary to CRVO (without considering the revised patient access scheme implemented in NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema) to give an ICER at the top end of the range usually considered cost effective.

Revised economic model submitted by the manufacturer during consultation

3.31 In response to the consultation on the appraisal consultation document the manufacturer submitted a revised cost–utility analysis addressing the Committee's concerns about the original model. The revised economic model included the ERG's preferred assumptions relating to 10% of patients being treated in their 'better-seeing eye', utilities from Czoski-Murray et al. (2009). The manufacturer also applied some alternative assumptions (see sections 3.33 to

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3.36) to present revised base-case cost-effectiveness estimates for ranibizumab compared with dexamethasone in both BRVO and CRVO.

3.32 The manufacturer considered that the ERG's approach to deriving utilities from Czoski-Murray et al. (2009) underestimated the utility gains associated with improving visual acuity. The manufacturer therefore provided an alternative to the ERG's derivation of utilities by applying a regression equation from the Czoski-Murray et al. (2009) publication to derive utilities for each of the 8 BCVA health states in a similar way to that employed in the NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration. The manufacturer also applied a 0.3 overall benefit of treating the 'worse-seeing eye' because it felt that a 0.1 benefit, as applied by the ERG, did not capture the difference in utility for people with blindness in their 'worse-seeing eye'.

3.33 The manufacturer did not apply an excess mortality risk specifically associated with RVO in its revised model because the available evidence was conflicting, and it considered the evidence base to be inconclusive. In addition, the manufacturer highlighted that an excess mortality risk had not been included in the evidence submitted for NICE's technology appraisal guidance on dexamethasone intravitreal implant in macular oedema secondary to retinal vein occlusion. However, the manufacturer did amend the model to include mortality risk associated with visual impairment in the 'worse-seeing eye' as originally suggested by the ERG (see section 3.26).

3.34 The manufacturer acknowledged the Committee's concerns about the use of pooled transition probabilities during months 7 to 24 of the BRAVO trial, which were originally used to account for the confounding effect of patients being treated with grid laser photocoagulation at the same time as treatment with ranibizumab. In its revised model, the manufacturer applied data for months 7 to 24 from only the ranibizumab arm of BRAVO to inform the transitions of all BRAVO patients.

3.35 The manufacturer's revised model included updated adverse event rates for year 2 for ranibizumab as well as updated adverse event rates for dexamethasone for year 1, based on 12-month outcomes from the GENEVA studies published since the manufacturer's original submission. In addition, the

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manufacturer considered that the dexamethasone re-treatment frequency included in the original model (every 6 months) was conservative and therefore applied a re-treatment frequency of 4 months to the revised model.

3.36 Finally, the manufacturer applied a lifetime time horizon instead of the 15-year time horizon included in the original submission in order to derive its base-case cost-effectiveness estimates. The manufacturer stated that this was consistent with the approach taken in NICE's technology appraisal guidance on dexamethasone intravitreal implant in macular oedema secondary to retinal vein occlusion.

3.37 The manufacturer highlighted in its consultation response that although patients with brisk afferent pupillary defect were excluded from the BRAVO and CRUISE studies, this only represents those at the more severe end of the ischaemic spectrum and therefore did not exclude those with milder ischaemia.

3.38 After consultation on the appraisal consultation document, the manufacturer responded to the Committee's concerns regarding the extent of bias generated by the differences in the duration of macular oedema between GENEVA and BRAVO/CRUISE. The manufacturer commented that the extent of bias was not known and that the implications for the ICER may be minimal. They also re-examined the reported mean durations of macular oedema in the GENEVA (dexamethasone) and BRAVO and CRUISE (ranibizumab) studies noting that in the GENEVA studies, the mean duration of macular oedema was assessed at a screening visit which occurred at least 1 month earlier than in the BRAVO and CRUISE studies. The manufacturer further noted that its cost-effectiveness analysis of ranibizumab compared with dexamethasone was already favourable to dexamethasone because the relative effectiveness of ranibizumab and dexamethasone was assessed at 3 months, and conservative assumptions related to the number of dexamethasone injections and the rate of adverse events associated with dexamethasone were used.

3.39 In their response to the appraisal consultation document consultation the manufacturer reiterated their view that bevacizumab is not a valid comparator because it does not satisfy the definition of a comparator as set out in NICE's guide to the methods of technology appraisal because, in their view, the use of bevacizumab is not routine or best practice, and because bevacizumab is not

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licensed for RVO. The manufacturer further highlighted that the studies included in the ERG's indirect comparison of ranibizumab with bevacizumab had methodological shortcomings and that the inclusion of the study by Russo et al. (2009) was inappropriate because standard deviations were not reported in this study for the values of change from baseline. The manufacturer considered the ERG's conclusion about the direction of bias in the indirect comparison to be overly speculative and not evidence-based. In addition the manufacturer reiterated its concerns over comparisons with an unlicensed drug that might compromise patient safety, further noting that the absence of a full pharmacovigilance programme (normally funded by the drug sponsor), would mean that the cost of safety surveillance would be a significant burden to the NHS and was not included in the ERG's cost-minimisation analysis. The manufacturer provided an estimate of the per-patient cost of a basic pharmacovigilance programme, which was submitted as commercial in confidence and cannot therefore be reported. Finally, the manufacturer highlighted that the ERG's use of a cost-minimisation analysis is fundamentally flawed and that it was not appropriate to assume equivalent safety and efficacy of ranibizumab and bevacizumab, an assumption required for cost-minimisation methodology, when this has not been established.

Evidence Review Group's comments on the manufacturer's revised model

3.40 The ERG noted the manufacturer's approach to applying the 'better-seeing eye' utilities from Czoski-Murray et al. (2009) to the model and agreed that this was appropriate because it provided utilities for each of the health states in the model rather than the ERG's smaller set of utility values (see section 3.32), and was consistent with the approach taken by the Assessment Group for NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration. The ERG considered the manufacturer's approach of applying a maximum utility gain of 0.3 from treatment of the 'worse-seeing eye'. The ERG noted that the manufacturer extrapolated the 0.1 utility loss estimated by Brown et al. (2001) to apply further loss in the 'worse-seeing eye'. However, the ERG considered that the evidence presented by Brown et al. (2001) suggested that further deterioration in visual acuity in the

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'worse-seeing eye' did not affect utility and therefore applying a 0.3 utility gain was not evidence-based. They also considered that it lacked face validity.

3.41 The ERG noted the manufacturer's response suggesting that the extent of bias towards ranibizumab in comparison with dexamethasone was overestimated (in the original ERG report). The ERG acknowledged that there is uncertainty surrounding the extent of bias but that this is difficult to quantify. With respect to duration of macular oedema at baseline, the ERG did not have access to data from BRAVO and CRUISE to adjust for the difference in the timing of measurement of duration of macular oedema compared with GENEVA. The ERG also noted that although the manufacturer's revised model uses data from months 7 to 12 of the ranibizumab arm of BRAVO to inform all transition probabilities from month 7 to 24, this assumes equivalent efficacy between dexamethasone and ranibizumab when given as needed. The ERG noted that it is not clear whether this assumption is conservative, and that evidence provided by the manufacturer from the BRAVO trial showed that there is a decline in ranibizumab's efficacy when given as needed rather than as monthly treatment.

3.42 The ERG considered the manufacturer's consultation response to dexamethasone re-treatment frequency and adverse events associated with dexamethasone. The ERG noted that the manufacturer's approach should have also modelled the effectiveness of dexamethasone re-treatment given less frequently than every 4 months (for example, every 5 months) and that the manufacturer did not take into account that a higher re-treatment frequency would result in a more stable efficacy for dexamethasone. In addition, the ERG agreed that a higher re-treatment frequency for dexamethasone would have the impact of increasing the number and severity of adverse events.

3.43 The ERG noted the manufacturer's response to the issue of ischaemic disease. The ERG agreed that the exclusion criterion in BRAVO and CRUISE of brisk afferent pupillary defect would not exclude patients with minor ischaemic disease. However, the ERG noted that none of the key trials used in the ERG's exploratory analysis, including BRAVO and CRUISE, reported data on the number of patients with baseline macular ischaemia. Therefore, the ERG highlighted that it could not be assumed that patients with ischaemia could have been included in BRAVO and CRUISE and stated that the effects of ranibizumab in the subgroup of patients with macular oedema secondary to ischaemic RVO were unknown.

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Patient access scheme as revised in the context of NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema

3.44 The manufacturer submitted a revised patient access scheme in 2013 for consideration in this appraisal (as revised in the context of NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema), in which it applied a revised discount to ranibizumab for all indications (see section 2.4). The manufacturer did not submit any additional clinical-effectiveness data but submitted an economic model that incorporated the revised patient access scheme discount and employed all of the revised assumptions from the manufacturer's response to consultation (outlined in more detail in sections 3.31 to 3.39). In summary these were as follows:

- deriving utilities from Czoski-Murray et al. (2009) for each of the 8 BCVA health states in a similar way to that employed in NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration by applying a regression equation from Czoski-Murray et al. (2009)
- applying a 0.3 overall utility benefit for treating the 'worse-seeing eye'
- including mortality risk associated with visual impairment as suggested by the ERG
- applying data for months 7 to 24 from only the ranibizumab arm of BRAVO to inform the transition probabilities of all BRAVO patients
- including updated adverse event rates for year 2 for ranibizumab as well as updated adverse event rates for dexamethasone for year 1
- applying a lifetime time horizon to be consistent with NICE's technology appraisal guidance on dexamethasone intravitreal implant for macular oedema secondary to retinal vein occlusion.

3.45 By applying all of their revised assumptions (see section 3.44), the manufacturer's revised base-case ICERs (with the revised patient access scheme as implemented in NICE's technology appraisal guidance on ranibizumab for

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treating diabetic macular oedema) for ranibizumab compared with dexamethasone were £2,370 and £6,995 per QALY gained for BRVO and CRVO respectively. For ranibizumab compared with best supportive care in CRVO the ICER was £13,851 per QALY gained, whereas for ranibizumab compared with grid laser photocoagulation in BRVO, the ICER was £23,073 per QALY gained.

3.46 The manufacturer performed a deterministic sensitivity analysis and found the model to be sensitive to the frequency of injections and follow-up visits; for example in BRVO, increasing the number of injections in year 2 (from 2.5 to 6) increased the ICER for ranibizumab compared with dexamethasone from £2,370 to £9,892 per QALY gained.

3.47 The manufacturer provided scenario analyses (one-way sensitivity analysis) which explored the effect of changing some of the parameters in the model individually. The manufacturer explored the effect of applying a 0.2 overall utility gain for treating the 'worse-seeing eye'. This increased the base-case ICERs of ranibizumab compared with dexamethasone from £2,370 to £3,029 per QALY gained for BRVO, and from £6,995 to £9,005 per QALY gained for CRVO. For ranibizumab compared with best supportive care in CRVO, the ICER increased from £13,851 to £18,332 per QALY gained. For ranibizumab compared with grid laser photocoagulation, the manufacturer's ICER increased from £23,073 to £30,778 per QALY gained.

3.48 Other scenario analyses included reducing the mean number of ranibizumab injections in year 2 (the revised number of mean injections was submitted as academic in confidence and cannot be presented). This reduced the ICERs of ranibizumab compared with dexamethasone by 54% in BRVO and by 58% in CRVO. A scenario which included longer follow-up data based on year 2 of the HORIZON extension study reduced the ICERs for ranibizumab compared with dexamethasone from £2,370 to £1,599 per QALY gained and from £23,073 to £20,911 per QALY gained for ranibizumab compared with grid laser photocoagulation in BRVO. The corresponding scenario analysis for CRVO was not presented.

3.49 The manufacturer also presented probabilistic sensitivity analyses and concluded that from the base-case results the probability that ranibizumab was cost effective when compared with grid laser photocoagulation in BRVO was 44.2% at

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a threshold of £20,000 per QALY gained and 58.6% at a threshold of £30,000 per QALY gained. For ranibizumab compared with best supportive care in CRVO, the probability of cost effectiveness was estimated by the manufacturer to be 67.9% and 82.0% at thresholds of £20,000 and £30,000 per QALY gained respectively.

ERG critique of manufacturer's revised base case with the patient access scheme as revised in the context of NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema

3.50 The ERG noted that the revised model used to inform the current patient access scheme submission is the same as that submitted as part of the manufacturer's response to the original consultation, but that not all issues raised by the Committee have been addressed. Therefore, the ERG's views outlined in sections 3.40 to 3.43 (relating to deriving utilities, transition probabilities, re-treatment frequency and adverse events associated with dexamethasone and ischaemic disease) still apply. Overall, the ERG accepted the manufacturer's approach to:

- modelling 90% of people in the model as being treated in their 'worse-seeing eye'
- the use and implementation of the 'better-seeing eye' utilities derived from Czoski-Murray et al. (2009)
- excess mortality associated with visual impairment in the 'worse-seeing eye'
- updated adverse events.

However, the ERG maintained that the available evidence relating to utility gain from treating the 'worse-seeing eye' suggests a utility decrement of 0.1 (rather than the manufacturer's assumption of 0.3) between the best and worst 'worse-seeing eye' BCVA health states. Therefore, the ERG provided amended exploratory cost-effectiveness estimates to include the assumption of a 0.1 utility decrement. For BRVO, this increased the manufacturer's base-case ICER for ranibizumab compared with grid laser photocoagulation

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from £23,073 to £44,713 per QALY gained. In the ERG's incremental analysis in BRVO, dexamethasone was extendedly dominated by ranibizumab (that is, the ICER for dexamethasone compared with grid laser photocoagulation was higher than for ranibizumab compared with grid laser photocoagulation) and the ICER compared with best supportive care was £44,713 per QALY gained. The ERG highlighted that there is considerable uncertainty in the comparisons of ranibizumab with grid laser photocoagulation and with dexamethasone as a result of the confounded data from BRAVO (grid laser photocoagulation was permitted in the ranibizumab arm after 3 months of treatment) used to inform the comparison with grid laser photocoagulation and the absence of a direct comparison with dexamethasone.

3.51 For ranibizumab compared with dexamethasone in BRVO, the ERG's amendment of including a 0.1 utility decrement increased the manufacturer's base-case ICER from £2,370 to £4,092 per QALY gained. The ERG performed the same amendment for CRVO, and the ICER for ranibizumab compared with best supportive care increased from £13,851 to £26,263 per QALY gained, and for ranibizumab compared with dexamethasone the ICER increased from £6,995 to £12,306 per QALY gained. In the ERG's incremental analysis for CRVO, dexamethasone was extendedly dominated by ranibizumab (that is, the ICER for dexamethasone compared with best supportive care was higher than for ranibizumab compared with grid laser photocoagulation) and the ICER for ranibizumab compared with best supportive care was £26,263 per QALY gained. The ERG highlighted that the absence of a direct comparison of ranibizumab with dexamethasone generates considerable uncertainty in these results. In particular, the manufacturer assumed that from month 7 onwards, the efficacy of dexamethasone is equivalent to ranibizumab when given as needed (rather than monthly). The ERG note that it remains unclear whether this assumption would lead to bias towards or against ranibizumab.

NICE Decision Support Unit report

3.52 Following the Committee's consideration of comparators in this appraisal, and in line with NICE processes (specifically section 3.5.49 of the guide to the single technology appraisals process), the NICE Board asked for additional work to be

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commissioned from the NICE Decision Support Unit (DSU) related specifically to the consideration of intravitreal bevacizumab as a comparator.

3.53 The DSU report considered 4 questions:

- What evidence is there relating to the pharmaceutical quality of reformulated bevacizumab as used in eye conditions in general?
- How widespread is intravitreal bevacizumab use in the UK?
- What is the evidence for efficacy of intravitreal bevacizumab in adults with RVO (and diabetic macular oedema) specifically?
- What evidence is there regarding adverse events for intravitreal bevacizumab in eye conditions in general?

3.54 The DSU report noted that the process of diluting and aliquoting bevacizumab into the smaller doses required for intravitreal injections requires a 'specials' licence issued by the Medicines and Healthcare products Regulatory Agency (MHRA) and can be performed by hospital pharmacists or on a larger scale by specialist units under tightly controlled conditions. The DSU identified Moorfields Pharmaceuticals (a manufacturing arm of Moorfields Eye Hospital NHS Foundation Trust) and Liverpool and Broadgreen University Hospitals pharmacy as the 2 major suppliers of intravitreal bevacizumab in the UK, both of which hold 'specials' licences. The DSU report highlighted that the greatest risk from reformulation of bevacizumab is infection such as endophthalmitis, which can lead to loss of vision or even the eye itself, and that there has been a warning issued about this by the US Food and Drug Administration (FDA). Reports of sterile endophthalmitis or uveitis by Moorfields to the MHRA have resulted in the recall of 27 batches of bevacizumab.

3.55 The DSU report investigated the extent of use of intravitreal bevacizumab in the UK by reviewing commissioning policy documents, data from the 2 major suppliers of intravitreal bevacizumab, and a survey of consultant ophthalmologists. The findings suggested that there is substantial use of intravitreal bevacizumab across the UK in eye conditions in general and that its use is even more widespread in private practice.

3.56 The report also reviewed the evidence relating to efficacy of intravitreal

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bevacizumab specifically in RVO. The DSU identified 5 RCTs that examined the effectiveness of bevacizumab on BCVA in people with RVO, 3 of which were in populations with CRVO; the remaining 2 studies were in BRVO. The studies all suggested that intravitreal bevacizumab appeared to confer some improvement in BCVA in both BRVO and CRVO compared with sham injection. However, because 3 of the studies were only available as conference abstracts, detailed data were not available. In addition, the DSU highlighted that interpretations of the findings should be made with caution because of the small number of studies with relatively small sample sizes and differences in participants' age, gender distribution and type of RVO. The studies also had relatively short follow-up durations (the maximum was 24 weeks).

3.57 The report assessed the evidence relating to adverse events associated with intravitreal bevacizumab in eye conditions in general. A total of 22 RCTs were identified, which evaluated the safety of bevacizumab compared with laser therapy, sham injection, triamcinolone, ranibizumab, pegaptanib and observational control. In addition, 67 observational non-RCT studies were included in the safety review of intravitreal bevacizumab. Overall, the DSU report commented that adverse event rates following intravitreal bevacizumab treatment were low when compared with other intravitreal treatments, sham injection and laser therapy and most of these studies were in people with AMD, diabetic macular oedema or RVO. Most outcomes were not significantly different between groups. The DSU report noted that higher rates of adverse events have been reported in the bevacizumab group in the head-to-head studies of intravitreal bevacizumab and ranibizumab (CATT and IVAN trials in AMD) and although this was not significant in the IVAN trial, when added to the meta-analysis with the CATT trial, the overall finding was statistically significant. Overall the DSU considered that the 22 RCTs offer the most robust assessment of adverse events. The DSU commented that the evidence on safety of intravitreal bevacizumab from observational studies was inconclusive. However, with respect to larger studies, observational data from Curtis et al. suggested no difference in the risk of adverse events between bevacizumab and ranibizumab, and another population-based case–control study reported no relationship between the risk of systemic events such as myocardial infarction, venous thromboembolism, stroke or congestive heart failure and the administration of intravitreal bevacizumab or ranibizumab.

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3.58 Comments on the DSU report consultation highlighted that the quality of reformulated bevacizumab might vary between studies and in clinical practice, and there are concerns about the reports of endophthalmitis. However it is unclear how this compares with ranibizumab. Consultees commented that there was insufficient evidence to evaluate the safety of intravitreal bevacizumab, while other consultees noted that the pooled analysis of IVAN and CATT trials, which compared ranibizumab and bevacizumab directly (in people with AMD), showed significantly higher serious systemic adverse events in the bevacizumab group. Some consultees noted that although there is some favourable evidence for efficacy of intravitreal bevacizumab for RVO in comparison with sham injection, the evidence is limited. However, some consultees noted that the use of intravitreal bevacizumab could be substantial but may have declined since the publication of NICE's technology appraisal guidance on dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion.

3.59 Full details of all the evidence are in the manufacturer's submission and the ERG report.

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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 visual impairment caused by macular oedema secondary to retinal vein occlusion (RVO) 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 heard from patient experts about the problems associated with visual impairment caused by macular oedema. It heard that the loss of vision has a significant effect on the independence of people with the condition. The patient experts also stated that the condition affects ability to work and hobbies such as reading and gardening. The patient experts acknowledged that although people may be worried about having an injection in the eye, they are willing to receive injections in order to keep their sight. The Committee agreed that loss of vision caused by macular oedema secondary to retinal vein occlusion seriously impairs health-related quality of life.

4.3 The Committee heard from clinical specialists that the current standard treatment for visual impairment caused by macular oedema secondary to branch RVO (BRVO) is grid laser photocoagulation but that in interim guidelines from the Royal College of Ophthalmologists it is only recommended after a period of 3 to 6 months following the initial event (obstruction of retinal veins) and following the absorption of the majority of the haemorrhage. The Committee heard from the clinical specialists that grid laser photocoagulation is not an option for people with central RVO (CRVO), because CRVO does not respond to grid laser photocoagulation (as outlined in the Royal College of Ophthalmologists' interim guidelines on RVO) and the current standard treatment is dexamethasone or anti-vascular endothelial growth factor (VEGF) drugs such as bevacizumab.

4.4 The Committee considered the comparators for the appraisal, and specifically bevacizumab intravitreal injection. It was aware that bevacizumab does not have a UK marketing authorisation for the treatment of RVO and heard from patient experts that they were concerned about using unlicensed treatments for which there was no formal post-marketing surveillance, particularly if there were

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alternatives that have a UK marketing authorisation. The Committee noted that a marketing authorisation is not a prerequisite for a comparator in a NICE technology appraisal. It noted that NICE's guide to the methods of technology appraisal, in recommending comparison with technologies that are 'best practice' or in 'routine use', is not intended to be restrictive but to emphasise the need for comparison with all relevant comparators; any medicine in routine use or considered to be best practice should be considered a comparator. The Committee was minded to conclude that bevacizumab fulfils the requirements for inclusion as a comparator but noted the advice from the NICE Board that this decision should be based on a careful consideration of its use in clinical practice for the condition concerned and, critically, a thorough assessment of its efficacy and safety.

4.5 The Committee considered the information in the Decision Support Unit (DSU) report on the product quality of reformulated bevacizumab. It was aware of consultation comments on the DSU report raising concerns on quality and reports of endophthalmitis and uveitis with intravitreal bevacizumab, although it was not clear how the number of reports compared with those observed with ranibizumab. The Committee also noted the comments from consultation on the DSU report that reformulation of pharmaceutical products is not an unusual practice and is routinely performed in many other circumstances under a 'specials' licence. The Committee noted that reformulating bevacizumab for intravitreal use requires a 'specials' licence from the Medicines and Healthcare products Regulatory Agency (MHRA) and that this means manufacturers must adhere to a range of conditions and inspections. The Committee was satisfied that there is some level of good manufacturing practice in place when pharmaceutical products are reformulated under a 'specials' licence and that such practice is not exceptional.

4.6 The Committee considered the evidence relating to the safety of bevacizumab as reported by the DSU. It was aware that in the 22 randomised controlled trials (RCTs) identified for age-related macular degeneration (AMD), diabetic macular oedema and RVO, adverse events were few compared with sham injection, laser photocoagulation and other intravitreal treatments. The Committee noted the pooled analysis from the IVAN and CATT trials (both in patients with AMD), which showed a statistically significantly higher rate of systemic adverse events in the bevacizumab group than in the ranibizumab group. However, it also noted

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observational data from a large study by Curtis et al. suggesting no difference in the risk of adverse events between bevacizumab and ranibizumab. It also noted a population-based case–control study, including over 90,000 patients, that reported no relationship between the risk of systemic events such as myocardial infarction, venous thromboembolism, stroke or congestive heart failure and the administration of intravitreal bevacizumab or ranibizumab. The Committee concluded that the evidence base relating to the safety of bevacizumab was sufficient to inform judgement of whether bevacizumab is an appropriate comparator.

4.7 The Committee considered the evidence base for the efficacy of bevacizumab in treating visual impairment caused by macular oedema secondary to BRVO and CRVO. It noted the small trials (2 in BRVO, 3 in CRVO) identified in the DSU report, of which 3 were published only as abstracts. The Committee agreed that all trials reported significant mean improvements in best corrected visual acuity (BCVA) for bevacizumab compared with sham injections, but because no direct comparisons of ranibizumab with intravitreal bevacizumab are currently available, a mixed treatment comparison would be needed to answer the question of relative effectiveness between the 2 treatments. The Committee noted that the DSU was not asked to address this question specifically. The Committee concluded that the available evidence was limited with small sample sizes and differences in study populations but on balance sufficient to inform judgement of whether bevacizumab is an appropriate comparator.

4.8 Having noted the available evidence and comments from consultation on the safety, efficacy and quality of intravitreal bevacizumab, the Committee concluded that bevacizumab is an appropriate potential comparator in this appraisal. However, the Committee further concluded that there is currently insufficient evidence to make robust comparisons with ranibizumab needed for a cost-effectiveness analysis.

Clinical effectiveness

4.9 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of ranibizumab. It noted that the main sources of evidence came from the BRAVO and CRUISE RCTs, which included patients with macular

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oedema secondary to BRVO and CRVO respectively. It also noted the evidence from the 12-month open-label extension of both trials, the HORIZON study. The Committee noted that the decision problem for the appraisal included people with or without retinal ischaemia. However it was aware that most patients with retinal ischaemia were excluded from the BRAVO and CRUISE trials, because patients with a brisk afferent pupillary defect (which equates to severe retinal ischaemia) were excluded. It heard from the clinical specialists and the manufacturer that this meant that there was no evidence of ranibizumab for treating visual impairment caused by RVO in patients with significant ischaemia.

4.10 The Committee noted that in both BRAVO and CRUISE ranibizumab was associated with statistically significant mean gains in BCVA in the treated eye compared with sham injection for the 6-month treatment phase. It also noted that ranibizumab was associated with sustained gains in BCVA at 12 months in both BRAVO and CRUISE, and that these were statistically significant ($p<0.01$ and $p<0.001$ respectively). The Committee was aware that ranibizumab could be used as needed in both arms of both trials from 6 months. In addition, the Committee was aware that in the BRAVO trial, grid laser photocoagulation was permitted after 3 months in both the sham group and the ranibizumab group, confounding the results of the treatment phase from month 3 onwards. Despite this, the Committee concluded that ranibizumab is a clinically effective treatment for visual impairment caused by macular oedema secondary to BRVO and CRVO compared with sham injection, if there is no significant retinal ischaemia.

4.11 The Committee considered the evidence for adverse effects associated with ranibizumab. It noted that the safety of ranibizumab had been shown previously in patients with wet AMD (NICE's technology appraisal guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration) and diabetic macular oedema (NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema). The Committee also noted that the overall frequency of adverse effects in the BRAVO and CRUISE trials at month 6 was low. It agreed that ranibizumab was safe and well tolerated in patients with macular oedema secondary to RVO.

4.12 The Committee noted that the BRAVO and CRUISE trials collected data on the effect of visual impairment on quality of life using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) questionnaire. It noted that both trials

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reported a statistically significant difference in NEI VFQ-25 score at month 6 between the ranibizumab and sham injection groups. The Committee concluded that treating patients with ranibizumab improves the quality of life of people with visual impairment caused by macular oedema secondary to RVO.

Cost effectiveness

4.13 The Committee considered the manufacturer's original economic model and the critique and exploratory analyses performed by the Evidence Review Group (ERG). It noted the manufacturer's original base-case incremental cost-effectiveness ratios (ICERs) of £8,600 and £20,500 per quality-adjusted life year (QALY) gained for ranibizumab compared with standard care for CRVO and BRVO respectively and the ICERs for ranibizumab compared with dexamethasone in CRVO and BRVO which were £7,200 and £5,500 per QALY gained respectively. The Committee broadly accepted the model structure, but was concerned by some of the uncertainties highlighted by the ERG around the assumptions used by the manufacturer. In particular, the Committee did not accept:

- the assumption that all patients would be treated in their 'better-seeing eye', having heard from clinical specialists that this is not the case in clinical practice, and that most patients in the CRUISE and BRAVO trials were treated in their 'worse-seeing eye' (see section 3.22)
- the manufacturer's use of 'better-seeing eye' utility values from the Brown study, without age adjustment (see section 3.27)
- the absence of a mortality risk associated with RVO in the model (see section 3.25)
- the use of pooled transition probabilities during months 7 to 12 of the BRAVO trial, which overestimated the efficacy of ranibizumab compared with sham injection (see section 3.23)
- the potential bias in the indirect comparison between ranibizumab and dexamethasone (both BRVO and CRVO), with different exclusion rules for ischaemia, patients with different durations of macular oedema and different severities in the trials of each drug (see section 3.24).

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The Committee concluded that the most plausible ICERs for ranibizumab compared with standard care and dexamethasone intravitreal implant, based on the manufacturer's base case modified appropriately by the ERG, were likely to range from £31,100 to £52,000 per QALY gained and would therefore be well in excess of £20,000 to £30,000 per QALY gained. It also noted that there was additional uncertainty about the cost-effectiveness estimates for ranibizumab in people with BRVO because grid laser photocoagulation was permitted after 3 months in both the sham and the ranibizumab groups, confounding the results of the treatment phase from month 3 onwards. The Committee proceeded to consider the revised model submitted by the manufacturer.

4.14 The Committee noted the manufacturer's revisions to its economic model submitted in response to consultation. It first noted the amendment to reflect the fact that most patients (90%) would be treated in their 'worse-seeing eye'. The Committee considered that this was consistent with the BRAVO and CRUISE trials and clinical practice, and concluded that this amendment was appropriate.

4.15 The Committee next considered the manufacturer's revised approach to deriving utilities for the 'better-seeing eye' from Czoski-Murray et al. (2009) for use in the economic model. It understood that these utilities would only apply to 10% of the people in the revised economic model which now assumed that 90% of people would be treated in their 'worse-seeing eye' (section 4.14). The Committee noted that the manufacturer had applied a regression equation from Czoski-Murray et al. (2009) to produce a finer degradation of the utilities. The Committee noted that the ERG accepted the manufacturer's use and implementation of the utilities as applied using the Czoski-Murray equation and further noted the provisional guidance from the rapid review of NICE technology appraisal guidance 237 (now published as NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema) in which the range of utility values was accepted to lie somewhere in between those estimated by Czoski-Murray and those from the Brown study. The Committee concluded that although uncertain, the use of utilities as applied using the Czoski-Murray equation was acceptable.

4.16 The Committee understood that the manufacturer's submission initially assumed that all people in the economic model would be treated in their 'better-seeing

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eye' and therefore did not apply a utility gain associated with treating the 'worse-seeing eye'. It noted that in the revised economic model (submitted in response to the appraisal consultation document) it was assumed that most people (90%) would be treated in their 'worse-seeing eye' in line with the ERG's suggestion. The Committee therefore considered the manufacturer's revised assumption of applying a 0.3 utility gain associated with treating the 'worse-seeing eye'. The Committee heard from the ERG that the manufacturer's assumption was based on an extrapolation of evidence from Brown et al. (2001). It understood that the ERG had used a gain of 0.1 from the Brown study in which utility values were collected separately for the 'worse-seeing' and 'better-seeing' eyes. The Committee considered that a 0.3 utility gain associated with treating the 'worse-seeing eye' seems high given that utility is driven primarily by the 'better-seeing eye', and therefore lacked face validity. It further noted that the manufacturer had originally suggested that no gain in utility would be obtained from treating the 'worse-seeing eye'. The Committee was also aware of the results of an analysis from NICE's technology appraisal guidance on dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion the details of which are commercial in confidence. The Committee concluded that a utility gain of 0.1 associated with treating the 'worse-seeing eye' was appropriate.

4.17 The Committee considered evidence supplied by the manufacturer during consultation relating to excess cardiovascular mortality associated with RVO, that is, the additional risk caused by cardiovascular complications associated with RVO, compared with the general population. The Committee noted that the excess mortality risk incorporated in the ERG base case was based on a paper from 2000 (Tsaloumas), which suggested that a person with RVO would have 1.6 times that of the general population. It noted that, of the papers referenced by the manufacturer in response to the original consultation, none suggested that overall mortality was lower for RVO patients than for the population at large. Some suggested it was greater. But the Committee was also aware that excess cardiovascular mortality had not been applied in NICE's technology appraisal guidance on dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion. The Committee concluded that the evidence on the risk of cardiovascular mortality associated with RVO was unclear, and therefore it need not be included in the base-case model to the degree applied in the original ERG report. However, it would remain an uncertainty in the

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analysis.

4.18 The Committee considered the manufacturer's response to the Committee's concerns about the use of pooled transition probabilities. The Committee was aware that the revised model used data from the ranibizumab arm of BRAVO to inform the transitions of all BRVO patients from month 7 to 24 which, in the view of the manufacturer, was a more conservative approach. The Committee noted that this had the effect of boosting the model's mean efficacy of the ranibizumab group after 6 months of treatment, because it assumes the same response to treatment for a person previously treated with ranibizumab as for a person naïve to ranibizumab treatment. It also noted that patients treated with grid laser photocoagulation or dexamethasone will experience the same benefit as patients treated with ranibizumab who are moving onto treatment with ranibizumab given as needed. The Committee heard from the ERG that because of the decline in efficacy of ranibizumab when given as needed in the extension arm of the trial, compared with monthly ranibizumab, it was unclear if the manufacturer's assumption was conservative. The Committee noted that the manufacturer's approach had minimal impact on the revised ICER for ranibizumab compared with dexamethasone in BRVO. The Committee acknowledged that there were advantages and disadvantages to the manufacturer and ERG's approaches. But it concluded that, given the lack of clear data, the approach taken by the manufacturer was appropriate.

4.19 The Committee discussed the manufacturer's revised assumption relating to adverse events. The Committee noted that the revised model included updated adverse event rates in year 2, which included iris neovascularisation as an adverse event for ranibizumab and dexamethasone and an updated estimate of the rate of cataract development for dexamethasone (based on 12-month outcomes from the GENEVA studies). The Committee noted the ERG's concern that it is not clear how the rate of iris neovascularisation was calculated for year 2. Although it acknowledged the ERG's concerns with the methods used to estimate adverse events in year 2, it cautiously accepted the updated safety data in the model.

4.20 The Committee considered the manufacturer's consultation response to the ERG's opinion that its exploratory economic comparison of ranibizumab with dexamethasone was biased in favour of ranibizumab. The Committee considered

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the manufacturer's points that the duration of macular oedema may have been underestimated by up to 1 month and that the rates of ischaemic disease were higher in the ranibizumab studies, and that the comparison at 3 months does not take into consideration the declining efficacy of dexamethasone. The Committee heard from the ERG that there may still be greater bias in favour of ranibizumab. This was because dexamethasone's efficacy starts declining at 2 months (which was incorporated in the analysis at 3 months) so in the first cycle of treatment dexamethasone's efficacy was in between that of the sham and ranibizumab treatment and was assumed to be equivalent to best supportive care in months 2 to 6, after which the same efficacy as ranibizumab was assumed. The Committee accepted that the relative effectiveness of ranibizumab and dexamethasone was uncertain and concluded that it was difficult to quantify any bias.

4.21 Having discussed the assumptions in the manufacturer's revised base-case model the Committee went on to discuss the ICERs produced from this model. It was aware that the manufacturer's revised model included the patient access scheme as revised in the context of NICE technology appraisal 274. It noted the ICERs for BRVO of £23,100 and £2,400 per QALY gained for ranibizumab compared with standard care (grid laser photocoagulation) and with dexamethasone respectively, and the base-case ICERs for CRVO of £13,900 and £7,000 per QALY gained for ranibizumab compared with best supportive care and dexamethasone respectively. The Committee noted that the ERG had accepted the manufacturer's assumptions relating to 90% of patients being treated in the 'worse-seeing eye', use of the 'better-seeing eye' utilities from Czoski-Murray et al. (2009) as modelled by the manufacturer, excess mortality associated with visual impairment in the 'worse-seeing eye', updated adverse events for year 2, and a lifetime time horizon. However, the Committee was aware that the ERG had undertaken an exploratory analysis on the revised model in which a maximum utility benefit of 0.1 from treating the 'worse-seeing eye', instead of the manufacturer's value of 0.3, had been applied. The Committee understood that this was the only difference in the calculation of the ICERs between the analyses. On the basis of its discussions relating to the maximum possible gain in utility from treating the 'worse-seeing eye' (section 4.16), the Committee concluded that its decision should be made on the basis of the ERG's adjustment to the manufacturer's calculations.

4.22 The Committee considered the ICERs for ranibizumab for CRVO calculated in the

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ERG's exploratory analyses. It noted that in this incremental analysis dexamethasone was extendedly dominated (that is, dexamethasone is dominated by a combination of 2 other alternatives, in this case best supportive care and ranibizumab) and therefore can be discounted from the analysis. Therefore, the Committee went on to consider the comparison of ranibizumab with best supportive care. It noted that, incorporating the patient access scheme (as revised in the context of NICE technology appraisal 274), ranibizumab was associated with an ICER of £26,200 per QALY gained compared with best supportive care in CRVO. The Committee was aware of remaining uncertainties regarding the possible confounding in the data resulting from both groups in the CRUISE trial receiving ranibizumab as needed from month 7 (section 4.10). It was also aware of the remaining uncertainty because of the absence of a direct comparison with dexamethasone, however on balance the Committee considered that the most plausible ICER for ranibizumab for visual impairment caused by macular oedema secondary to CRVO was between the £20,000 and £30,000 per QALY gained thresholds. It could therefore be considered a cost-effective use of NHS resources. The Committee therefore concluded that ranibizumab should be recommended as an option for treating visual impairment caused by macular oedema following CRVO. However, there remained uncertainties because of the absence of a direct comparison with dexamethasone.

4.23 The Committee considered the ICERs calculated in the ERG's exploratory analyses for ranibizumab for BRVO. The Committee noted that the key comparison was standard care with laser photocoagulation, rather than with dexamethasone, which is only recommended when laser treatment is inappropriate (NICE's technology appraisal guidance on dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion). The Committee therefore considered the ERG's exploratory ICER of £44,800 per QALY gained for ranibizumab compared with standard care. The Committee was aware that people receiving ranibizumab in the BRAVO trial could receive grid laser photocoagulation from month 3 and that this represented a significant confounding factor in both the manufacturer's and the ERG's calculations of the ICER for BRVO compared with standard care. It therefore considered that this ICER would be an underestimate of the most plausible ICER. The Committee concluded that the most plausible ICER for ranibizumab compared with standard care in treating BRVO was in excess of £44,800 per QALY gained. It further concluded that ranibizumab could not be recommended

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as an option for treating visual impairment caused macular oedema following BRVO when laser photocoagulation is an appropriate treatment option.

4.24 The Committee next considered the population with BRVO for whom grid laser photocoagulation is not an option. It considered that this population would include both those for whom grid laser photocoagulation has not been beneficial and those for whom grid laser photocoagulation is not a suitable treatment. It was aware that NICE's technology appraisal guidance on dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion had accepted the extent of macular haemorrhage as the definition for the subgroup of people for whom grid laser photocoagulation is not a suitable treatment option. Noting the Royal College of Ophthalmologists' 2010 Interim Guidelines on Retinal Vein Occlusion in which grid laser photocoagulation is only recommended following absorption of the majority of haemorrhage (section 4.3), the Committee accepted the extent of macular haemorrhage as the definition of the group of people for whom grid laser photocoagulation is not an option. The Committee understood that, when grid laser photocoagulation is not an option, the comparator in this analysis would be dexamethasone. It considered the ERG's exploratory analysis in which the ICER was £4,100 per QALY gained for ranibizumab compared with dexamethasone. Consistent with its previous conclusions it recognised that this ICER would be subject to uncertainty because of the absence of a direct comparison between ranibizumab and dexamethasone and because of confounding in the BRAVO trial. However, the Committee remained satisfied that the most plausible ICER would be below £20,000 per QALY gained. The Committee therefore concluded that ranibizumab should be recommended as an option for treating visual impairment caused by macular oedema following BRVO when grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage.

4.25 The Committee discussed how innovative ranibizumab is in its potential to make a significant and substantial impact on health-related benefits. It agreed that anti-VEGF treatments were a substantial improvement over previous treatments, but considered that this improvement applied to the class of drugs, including bevacizumab. It stated that the innovation was in the scientific step forward, not the act of licensing. In addition the Committee was not aware of any substantial benefits of ranibizumab over its comparators that would not be already captured into the QALY estimation in the modelling.

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4.26 The Committee considered whether there were any equalities considerations affecting population groups protected by equality legislation and concluded that there were no equality issues relating to this appraisal in the guidance.

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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 paragraph above. This means that, if a patient has visual impairment caused by macular oedema secondary to retinal vein occlusion and the healthcare professional responsible for their care thinks that ranibizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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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 macular oedema secondary to retinal vein occlusion should be conducted.

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7 Appraisal Committee members and NICE project team

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 4 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.

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

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Gary McVeigh
Vice chair of Appraisal Committee C, Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr David Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett

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Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler
Lay Member

Dr Mary Cooke
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Dr Chris Cooper
General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome
Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

Dr Christine Davey
Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips
Director, Public Policy and Advocacy NW Europe, BD, Oxford

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

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Dr Wasim Hanif
Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

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Dr Janice Kohler
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Director, Health Economics and Outcomes Research, BD, Oxford

Henry Marsh
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Professor Eugene Milne
Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Dr Neil Myers
General Practitioner, Glasgow

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Professor Katherine Payne
Professor of Health Economics, University of Manchester

Dr Danielle Preedy
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Dr Martin Price
Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

Alan Rigby
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Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi
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Dr John Stevens
Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield

Dr Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman
Professor of Health Economics, Brunel University, London

Dr Judith Wardle
Lay Member

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.

Christian Griffiths
Technical Lead

Joanne Holden
Technical Adviser

Lori Farrar
Project Manager

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8 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ-Technology Assessment Group (BMJ-TAG):

- Edwards SJ, Barton S, Trevor N et al. Ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO): A Single Technology Appraisal, July 2011

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 (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturer or sponsor:

- Novartis Pharmaceuticals

Professional or specialist and patient or carer groups:

- Royal National Institute of Blind People (RNIB)
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal College of Physicians

Other consultees:

- Department of Health
- Welsh Assembly Government

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- Wirral PCT

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

- BNF
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Allergan
- Roche Products
- BMJ Group
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on ranibizumab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Jonathan Gibson, Consultant Ophthalmologist, nominated by Royal National Institute of Blind People – clinical specialist
- Ian Pearce, Consultant Ophthalmologist, nominated by The Royal College of Ophthalmologists – clinical specialist
- Sobha Sivaprasad, Consultant Ophthalmologist, nominated by Novartis Pharmaceuticals – clinical specialist
- Rita Keeley, nominated by Royal National Institute of Blind People – patient expert
- Steve Winyard, nominated by Royal National Institute of Blind People – patient expert

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.

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- Novartis Pharmaceuticals

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Update information

May 2024: The wording of the recommendation describing the patient access scheme (see section 1.1) and in section 2.4 has been updated to include procurement information about ranibizumab biosimilars.

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