NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Ranibizumab for the treatment of diabetic macular oedema (Rapid Review of Technology Appraisal 237)

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer and the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- Are the utility values estimated from Czoski-Murray et al. (2009), in which members of the UK general public valued levels of visual impairment that were simulated by custom-made contact lenses, the most appropriate for measuring health-related quality of life in patients with diabetic macular oedema who receive treatment in the better-seeing eye?
- Has the manufacturer's rapid review submission made appropriate assumptions in its economic model about the amount of ranibizumab treatment (14 injections over 3 years) that patients would receive?
- The manufacturer's base-case model assumes that only one eye is treated (better-seeing eye) and applies a multiplier of 1.5 to approximate the cost-effectiveness of treating both eyes. The ERG developed an alternative approach, which makes explicit assumptions about the number of patients treated in their better-seeing eye, worse-seeing eye, or both eyes along with assumptions about the associated costs and QALYs. Which approach is more appropriate?

- The Committee in NICE technology appraisal guidance 237 considered that the manufacturer's model over estimated the degree of glycaemic control that would be expected in people treated in clinical practice in the UK. Do the Committee agree with the manufacturer that it is not appropriate to consider the cost effectiveness of ranibizumab in patients with poorer glycaemic control because of the uncertainty associated with the small patient numbers in this subgroup?
- The manufacturer's subgroup analyses according to retinal thickness use central retinal thickness rather than central foveal thickness as the measure of retinal thickness and categorised patients into two subgroups rather than three subgroups used in NICE technology appraisal guidance 237. Is this approach appropriate?

1 Rapid Review Submission

1.1 The manufacturer of ranibizumab has agreed a revised patient access scheme with the Department of Health, in which a simple discount of [redacted] on the list price of ranibizumab is offered. This patient access scheme is applied in the manufacturer's revised economic model.

1.2 NICE technology appraisal guidance 237 (TA 237, section 4.29) describes six concerns that were raised by the Committee in regard to the manufacturer's economic model. The manufacturer has submitted an amended economic model as part of its rapid review submission which attempts to address these concerns. A summary of the Committee's concerns and the manufacturer's response is provided sections 1.3 to 1.8 below.

1.3 Treating both eyes

- Committee's concern: by not accounting for the need to treat both eyes in a large proportion of people with diabetic macular oedema, the manufacturer's revised model

underestimated the benefits and – to a greater degree – the costs of treatments. The Committee noted its preference for a scenario that simulated treatment in both eyes for 35% of people because it provided a more realistic reflection of likely clinical practice. This scenario resulted in an incremental cost effectiveness ratio (ICER) that was almost 50% higher than the revised basecase which simulated treatment in the better-seeing eye (BSE).

- Manufacturer's approach in the rapid review submission: An ICER for treatment of both eyes was approximated by multiplying the ICER for the BSE by 1.5.

1.4 Range of utility values

- Committee's concern: the range of utility values used in the manufacturer's revised model (taken from the RESTORE trial) was broader than would be expected according to the assumptions of the model.

- Manufacturer's approach in the rapid review submission: the utility values estimated in a study by Czoski-Murray et al. (2009) are considered to be the Committee's preferred utility values (see table 3). In this study, members of the UK general public valued levels of visual impairment that were simulated by custom-made contact lenses, using the time trade-off method. Participants wore the same lenses in both eyes, so the resulting utility values reflected bilateral impairment of vision. Therefore, the manufacturer considered that these values were most appropriate for assessing the approximate cost effectiveness of treatment in both eyes.

1.5 Amount of ranibizumab treatment

- Committee's concern: The model underestimates the amount of ranibizumab that people with diabetic macular oedema are likely to need over time. The Committee considered that basing the number of injections for year 2 of the model's ranibizumab monotherapy arm on observed experience in the DRCR.net study overlooks the fact that the trial participants also received laser photocoagulation, which clinicians believe may have a ranibizumab-sparing effect. The declining number of ranibizumab injections assumed in years 3 and 4 is not evidence-based, and is unlikely to lead to stable vision during that period, as assumed. It may also be unrealistic to assume that ranibizumab treatment will not continue beyond 4 years.

- Manufacturer's approach in the rapid review submission: Based on the results of the RESTORE extension study which showed that the number of ranibizumab injections declined over 3 years, the manufacturer assumed that patients received 7 injections in year 1, 4 injections in year 2 and 3 injections in year 3, a total of 14 injections (compared with 13 injections in the previous submission for TA 237). The manufacturer also conducted a threshold analysis to assess the maximum number of injections per patient that could be administered over the time horizon of the model whilst maintaining an ICER below £30,000 per quality-adjusted life year (QALY) gained.

1.6 Relative treatment benefit of ranibizumab:

- Committee's concern: the model's assumption that the relative benefit achieved during the treatment phase lasts

indefinitely is unrealistic. The Committee commented that if NICE technology appraisal guidance 155 is considered a precedent for this approach, then it should be noted that the model in that appraisal had a shorter time horizon, which limited the Committee's uncertainty about extrapolating treatment effects into the future.

- Manufacturer's approach in the rapid review submission: to limit the uncertainty about extrapolating the relative benefit of ranibizumab treatment, the time horizon of the model is reduced from 15 years to 10 years. The manufacturer also presented a threshold analysis to explore the highest rate of worsening vision in the ranibizumab treatment arm whilst maintaining an ICER below £30,000 per QALY gained. To do this, the manufacturer assumed that best corrected visual acuity (BCVA) improved in 2.5% of patients and worsened in 5.5% of patients per 3-month cycle in the ranibizumab arm from year 4 onwards, compared to a 2.5% improvement and 3.5% deterioration in the laser photocoagulation arm.

1.7 Different numbers of treatment and monitoring visits:

- Committee's concern: the model applies different assumptions about treatment visits and monitoring visits for people treated with ranibizumab and those treated with laser photocoagulation. The Committee considered the ERG's argument that the manufacturer's model favoured ranibizumab by assuming that a visit for treatment with ranibizumab would double as a monitoring visit, but not assuming the same for laser photocoagulation. The Committee was unaware of any clinical evidence that justifies this difference, as the manufacturer had not

explained it in its original submission or in consultation comments. The Committee therefore concluded that it would be more realistic to adopt similar assumptions for both treatment arms.

- Manufacturer's approach in the rapid review submission: maintain that laser photocoagulation is predominantly delivered in a 'two-stop' clinic arrangement where patients assessed as requiring treatment, return for a separate laser clinic visit; and that ranibizumab treatment is predominantly delivered in a 'one-stop' visit. However, the manufacturer acknowledged that practice probably varies across centres in the NHS and that little published evidence exists on this issue. The manufacturer therefore assumed that treatment visits for both ranibizumab and for laser photocoagulation double as monitoring visits. The total number of treatment and monitoring visits are presented in table 1.

Table 1: Treatments, treatment visits and monitoring visits in the rapid review submission

Novartis rapid review submission	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Total**
ranibizumab injections	7	4	3	0	14
OP treatment visit	7	4	3	0	14
OP dedicated monitoring visit	5	4	3	2	14
OP total visits	**12**	**8**	**6**	**2**	**28**
laser treatments	2	1	1	0	4
OP treatment visit	2	1	1	0	4
OP dedicated monitoring visit	2	3	3	2	10
OP total visits	**4**	**4**	**4**	**2**	**14**

1.8 Glycaemic control subgroups:

- Committee's concern: the manufacturer's model over estimated the degree of glycaemic control that would be expected in people treated in clinical practice in the UK. The Committee observed that a subgroup analysis provided as part of the manufacturer's original submission in TA 237 had suggested that restricting analysis to trial participants with good glycaemic control (haemoglobin A1c (HbA_{1c} < 8%) produced a much lower ICER than the ICER based on the group of people with poor control (HbA_{1c} ≥ 8%). The Committee considered these findings exploratory because of the relatively small sample sizes, and agreed with consultation comments received from clinical specialists that it would not be appropriate to restrict the use of ranibizumab to individuals with lower HbA_{1c} values. However, the Committee took this as plausible evidence that the cost effectiveness of ranibizumab would be less favourable in people with worse glycaemic control. Therefore, the Committee concluded that the manufacturer's model would probably generate a higher ICER if it reflected the population seen in routine clinical practice.

- Manufacturer's approach in the rapid review submission: this issue is not addressed in the manufacturer's rapid review submission. The manufacturer maintains that the cost effectiveness analyses across these subgroups require careful interpretation because of the small sample sizes, which result in a very small number of patients in extreme health states influencing the results.

1.9 The manufacturer's revised model focused solely on the comparison of ranibizumab monotherapy with laser photocoagulation. The manufacturer presented separate ICERs for the treatment of the BSE and for both eyes (bilateral treatment). It estimated that ranibizumab was associated with a BSE ICER of £14,137 per QALY gained and a bilateral ICER of £21,205 per QALY gained in the base-case analysis. The manufacturer estimated that an additional 4 injections of ranibizumab can be delivered in years 4 to 9 (resulting in a total of 18 injections) for the bilateral ICER to remain below £30,000 per QALY gained. The manufacturer also estimated that the rate of deterioration in BCVA for patients treated with ranibizumab from year 4 onwards would need to be more than 1.5 times higher than that for patients treated with laser photocoagulation for the bilateral ICER to remain below £30,000 per QALY gained. The manufacturer conducted a number of one-way sensitivity analyses which suggested that the model was most sensitive to changes to the time horizon and utility values. When the time horizon was limited to 5 years the bilateral ICER was £41,568 per QALY gained. When utility values from the better-seeing eye study by Lloyd et al. were used, the bilateral ICER was £43,716 per QALY gained. No probabilistic sensitivity analyses were conducted by the manufacturer.

1.10 The manufacturer's rapid review submission included additional subgroup analyses according to the degree of retinal thickness. In NICE technology appraisal guidance 237, the manufacturer presented subgroup analyses according to three categories of central foveal thickness (< 300 micrometres, 300–400 micrometres and > 400 micrometres). This analysis was provided in response to comments from clinical specialists, suggesting that laser photocoagulation may be less effective in a thicker, more oedematous retina. For the rapid review, the manufacturer

presented subgroup analyses based on central retinal thickness, arguing that this provides a more reliable measure of retinal thickness than central foveal thickness. The manufacturer also acknowledged that the pattern of cost effectiveness estimates for the three subgroups defined by central foveal thickness in TA 237 was erratic and may have been driven by the small sample sizes. Therefore, the manufacturer pooled the two subgroups with lower values of central retinal thickness to create two subgroups (< 400 micrometres and ≥ 400 micrometres) of similar size. The manufacturer presented post-hoc tests of the statistical significance of differences in clinical outcome according to baseline central retinal thickness, which suggested that laser photocoagulation was less effective in patients with central retinal thickness of > 400 micrometres ($p < 0.01$). The manufacturer also made adjustments to the effectiveness and treatment frequency parameters for the two subgroups in the model. A summary of the ICERs for these two subgroups as well as the < 300 micrometres and 300–400 micrometres subgroups is presented in table 2.

Table 2. Manufacturer's subgroup analyses according to central retinal thickness

Central retinal thickness (CRT)	**ICER per QALY gained** **(Ranibizumab vs Laser photocoagulation**	
	BSE	**Bilateral**
≥ 400 micrometres	£8,881	£13,322
< 400 micrometres	£28,861	£43,292
300–400 micrometres	£25,665	£38,497
< 300 micrometres	£47,030	£70,545

2 ERG's commentary

2.1 The ERG commented that the manufacturer had correctly implemented the revised patient access scheme for ranibizumab and also the majority of the changes described in table 1 in order to address the Committee's concerns from TA 237.

BSE and worse-seeing eye (WSE) utility values

2.2 The ERG noted that the manufacturer's rapid review submission adopted utility values estimated in a study by Czoski-Murray et al. (2009). This study developed a regression model to estimate the relationship between BCVA (measured by the LogMAR [logarithm as the minimal angle of resolution] scale) and utility, with an adjustment for age. This regression model was subsequently used by the manufacturer to develop utility values for each of the 8 BCVA health states (defined by ETDRS scale) after converting the upper and lower limits of the ETDRS scale to its LogMAR equivalent. However, the ERG considered that the manufacturer's conversion from the ETDRS scale to LogMAR values may have been incorrect for 3 of the 8 values (Table 3). The manufacturer's

and the ERG's alternative LogMAR conversions, along with their respective estimated mean utility values are presented in table 3. When the ERG applied these alternative utility values to the manufacturer's revised model, the ICERs for treating the BSE or both eyes increased slightly to £14,473 and £21,710, respectively.

Table 3. Utility values from Czoski-Murray et al. calculated for the 8 BCVA health states (mean age of 65)

	Manufacturer's LogMAR conversion			ERG's LogMAR conversion		
BCVA (ETDRS scale)	**Lower**	**Upper**	**Manufacturer's mean utility values**	**Lower**	**Upper**	**ERG's mean utility values**
1: 86-100	-0.1	-0.3	0.869	0.0	-0.3	0.850
2: 76-85	0.2	0.0	0.758	0.2	0.0	0.758
3: 66-75	0.5	0.3	0.648	0.4	0.2	0.685
4: 56-65	0.6	0.4	0.611	0.6	0.4	0.611
5: 46-55	0.8	0.6	0.537	0.8	0.6	0.537
6: 36-45	1.0	0.8	0.464	1.0	0.8	0.464
7: 26-35	1.2	1.0	0.390	1.2	1.0	0.390
8: 0-25	1.2	n.a.	0.353	1.6	1.2	0.353

2.3 The ERG conducted further exploratory analyses to explore whether the utility values used by the manufacturer were appropriate for patients who only have their BSE treated. The ERG identified a study (Brown, 1999) that measured BCVA-related utility values using the time trade-off method in 325 US patients with impaired vision (Snellen scale 20/40) in at least one eye. This study produced BSE utility values that ranged from 0.920 to 0.540 for the 8 health states defined by BCVA. The ERG noted that the range in utility values for the BSE was narrower in the Brown study compared with the Czoski-Murray et al. study and that both utility

functions were reasonably linear for changes in the BCVA health states. The ERG also noted from the Brown study that, among patients who had good vision in their BSE, there was no strong relationship between vision in the WSE and health-related quality of life and that this suggested that changes in BCVA in the WSE would have a minimal impact on a patient's utility.

2.4 To explore how much the vision in a patients' WSE contributes to overall utility, the ERG conducted a number of scenario analyses. These analyses considered the range of utility values for the BSE (taken from Czoski-Murray et al.) from the health states reflecting the best to worst BCVA (0.850 – 0.353 = 0.497). The ERG then apportioned a percentage of this range to changes in the BCVA of the WSE. To do this, the ERG applied percentages of 0%, 15%, 30%, 50%, 75% and 100% in six scenarios. For example, scenario 1 assumed that changes in the BCVA of the WSE have no impact (0%) on quality of life, scenario 3 assumed a HRQoL function where changes in the BCVA of the WSE have 30% of the range of changes in the BCVA of the BSE (i.e. a range of 30%*0.497=0.149) and scenario 6 assumed a HRQoL function where changes in the BCVA of the WSE have 100% of the range of changes in the BCVA of the BSE (i.e. a range of 0.497, suggesting that changes in the BCVA in the WSE have the same impact on quality of life as changes in the BSE). The ERG assumed a linear function for the intermediate BCVA states (2 to 7) in accordance with the original BSE utility values estimated from Czoski-Murray et al. A summary of the utility values for the 8 BCVA states in each of these scenarios is presented in table 4.

Table 4. HRQoL by BCVA in the unilaterally treated WSE (extracted from ERG's amended economic model)

BCVA state (ETDRS)	Scenario 1: 0%	Scenario 2: 15%	Scenario 3: 30%	Scenario 4: 50%	Scenario 5: 75%	Scenario 6: 100%
1: 86-100	0.850	0.850	0.850	0.850	0.850	0.850
2: 76-85	0.850	0.839	0.829	0.815	0.797	0.779
3: 66-75	0.850	0.829	0.807	0.779	0.744	0.708
4: 56-65	0.850	0.818	0.786	0.744	0.690	0.637
5: 46-55	0.850	0.807	0.765	0.708	0.637	0.566
6: 36-45	0.850	0.797	0.744	0.673	0.584	0.495
7: 26-35	0.850	0.786	0.722	0.637	0.531	0.424
8: 0-25	0.850	0.775	0.701	0.602	0.477	0.353
Utility range from BCVA states 1-8	0% * 0.497 = 0	15% * 0.497 = 0.075	30% * 0.497 = 0.149	50% * 0.497 = 0.248	75% * 0.497 = 0.373	100% * 0.497 = 0.497

BSE, WSE and bilateral treatment ICERs

2.5 In exploratory analyses, the ERG provided an alternative approach to applying a 1.5 bilateral multiplier to the BSE ICER in order to estimate bilateral ICERs reflecting treatment of both eyes. This involved making explicit assumptions about the impact on costs and outcomes of adapting the model to consider treatment of both eyes. For this, the ERG combined the six scenarios described in section 2.4 with further exploratory analyses on the proportion of patients who would be treated in the BSE, WSE or both eyes. The scenarios explored by the ERG included the following assumptions:

- Based on the RESTORE trial, where [redacted] of patients had their WSE treated, [redacted] of patients are not eligible for bilateral treatment and only have their BSE treated, with the

associated utility values reflecting BCVA in the BSE taken from Czoski-Murray et al. (ERG's adjusted values) and the costs of severe visual impairment included.

- [redacted] of patients only have their WSE treated, with an associated WSE HRQoL function for each of the six scenarios described in section 2.4 and the costs of severe visual impairment removed.

- Based on figures presented by the manufacturer, 35% of patients receive treatment in both eyes. The ERG also assumed that the same absolute impact on QALYs results from changes in the BCVA of the WSE when it is bilaterally treated as when it is unilaterally treated. The QALYs gained from bilateral treatment are estimated by adjusting the QALYs gained for the BSE according to the impact of BCVA in the WSE on HRQoL for each of the six scenarios described in section 2.4. The treatment costs of ranibizumab are doubled and the costs of severe visual impairment are included. However, it is assumed that the costs of treatment and monitoring visits remain unchanged.

The ERG combined cost and QALY estimates from the three scenarios as a weighted average (split on a [redacted]:35% basis for BSE: WSE: bilateral treatment) and calculated the resultant pooled ICER for each of the six scenarios described in section 2.4 (see table 5).

Table 5. ERG's exploratory analyses according to treatment in the BSE, WSE or both eyes (Czoski-Murray et al. utility values)

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	WSE	Bilateral*	Mean	BSE	WSE	Bilateral*	Mean	Difference	ICERs
	[redacted]	[redacted]	35%		[redacted]	[redacted]	35%			
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
QALYs										
SA1 (0%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,712
SA2 (15%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,843
SA3 (30%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,999
SA4 (50%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,398
SA5 (75%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,411
SA6 (100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,585
* Bilateral QALYs calculated as BSE QALYs + Change in WSE QALYs from scenario 1. For example, in scenario 2 (15% change), ranibizumab bilateral QALYs are calculated as [redacted]										

2.6 The ERG repeated this analysis but replaced the utility values estimated from Czoski-Murray et al. with those taken from the study by Brown et al. This resulted in ICERs ranging from £50,879 per QALY gained in scenario 1 to £21,054 per QALY gained in scenario 6.The ERG also repeated this analysis but increased the proportion of patients receiving bilateral treatment on the basis of [redacted] of patients in the RESTORE trial with visual impairment in the second eye of ≤ 78 letters. When utility values from Czoski-Murray et al. were used, the ICERs ranged from £29,868 per QALY gained in scenario 1 to £15,433 per QALY gained in scenario 6. When utility values from Brown et al. were used, the ICERs ranged from £38,267 per QALY gained in scenario 1 to £19,970 in scenario 6.

2.7 The ERG commented that based on the results of the Brown study, which suggested that BCVA of the WSE has minimal impact on patient's HRQoL, the ICERs from scenarios 4 to 6 were less

plausible than scenarios 1 to 3. The ERG also commented that the scenario which considered treatment of the WSE only did not take into account the possible gain in HRQoL that would arise from a reduced fear of blindness if the WSE improves with treatment but remains the WSE.

Other issues

2.8 The ERG noted that the manufacturer had revised the number of ranibizumab injections in years 1, 2 and 3 of the model on the basis of an extension study to the RESTORE trial, resulting in a total of 14 injections over 3 years. However, the ERG commented that, because the number of ranibizumab injections was increased from 2 to 3 in year 3, it was unclear why the number of injections was reduced from 1 to 0 in year 4.

2.9 The ERG noted that the manufacturer did not provide further subgroup analyses according to the level of glycaemic control because of the uncertainty associated with the small patient numbers. However, although the ERG agreed that the results of these analyses may have been influenced by small number of patients in the extreme health states influencing the results, they suggested that this issue could have been addressed within a probabilistic model rather than a deterministic model presented by the manufacturer in its rapid review submission. When the ERG ran the probabilistic model, the subgroup with good glycaemic control (HbA_{1c} < 8%) produced a BSE ICER of £12,895 per QALY gained for ranibizumab monotherapy compared with laser photocoagulation. The subgroup with poorer glycaemic control (HbA_{1c} ≥ 8%) produced a BSE ICER of £21,560 per QALY gained when compared with laser photocoagulation.

2.10 The ERG commented that it was able to replicate most of the manufacturer's subgroup analyses according to central retinal thickness. The ERG noted that, although the modelling for the subgroup with thicker retina (CRT ≥ 400 micrometres) restricted the patient baseline BCVA distribution to ≤ 75 letters, the modelling for the subgroup with thinner retina (CRT < 400 micrometres) did not. When the ERG restricted the baseline BCVA distribution to ≤ 75 letters, the BSE ICER for this subgroup increased slightly to £29,666 per QALY gained. However, the ERG was unable to replicate the results for the subgroup with central retinal thickness of < 300 micrometres, producing a higher BSE ICER of £66,453 per QALY gained. The ERG commented that these discrepancies emphasise the importance of applying the subgroup specific baseline BCVA distribution for these analyses.

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