Ranibizumab for the treatment of macular oedema caused by retinal vein occlusion

ERG's critique of patient access scheme (PAS) submission

BMJ Technology Assessment Group

Evidence Review Group (ERG) critique of Novartis' patient access scheme (PAS) submission to the Committee appraising ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO)

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Novartis has submitted a financially-based patient access scheme (PAS), outlined in the document forwarded to the National Institute for Health and Clinical Excellence (NICE) dated 11th January 2013. The PAS involves a simple discount of [redacted] to the list price of ranibizumab. In addition, as requested in section 4.3 of NICE's PAS submission template, the manufacturer has provided a revised economic base case. The manufacturer's revised base case incorporates updates to the manufacturer's economic model based on assumptions considered most plausible by the Appraisal Committee.

The Evidence Review Group (ERG) notes that the Appraisal Committee raised several concerns regarding the manufacturer's original economic evaluation:

4.14 The inappropriateness of the assumption that all patients would be treated in their best seeing eye (BSE);

4.15 The absence of age adjustment in the utility values used;

4.16 The substantial impact on the incremental cost-effectiveness ratio (ICER) of the use of pooled transition probabilities in ranibizumab versus grid laser photocoagulation (GLP) in branch RVO (BRVO);

4.18 The absence of a mortality risk associated with RVO;

4.20 The potential bias in the comparison between ranibizumab and dexamethasone in central RVO (CRVO);

4.21 The exclusion of bevacizumab, a comparator likely to display equal efficacy to ranibizumab in CRVO;

4.22 The unfeasibility of a comparison of ranibizumab and GLP due to the highly confounding nature of the data available for this comparison;

4.23 The potential bias and uncertainty in the comparison of ranibizumab with dexamethasone in BRVO;

4.24 The exclusion of bevacizumab, a comparator likely to display equal efficacy to ranibizumab in BRVO.

The ERG notes that the revised model used to inform the manufacturer's current PAS submission is equivalent to that submitted by the manufacturer on 15th December 2011 in response to the ACD issued by NICE.[1] The revised model has been amended in response to the ACD, but not all issues raised by the Appraisal Committee have been addressed:

4.14 The economic model has been adjusted to assume that 90% of patients receive treatment in their worse seeing eye (WSE);

4.15 Utility values have been derived from a regression equation developed by Brazier *et al*.[2] which incorporates age as a covariate;

4.16 The use of pooled transition probabilities in the comparison of ranibizumab and GLP has been superseded by the use of data from the ranibizumab arm of BRAVO to inform all model transitions from month 7 onwards;

4.18 The manufacturer has suggested that this concern is not justified;

4.20 The manufacturer has suggested that this concern is not justified;

4.21 The manufacturer has suggested that this concern is not justified;

4.22 The manufacturer has suggested that this concern is not justified;

4.23 The manufacturer has suggested that this concern is not justified;

4.24 The manufacturer has suggested that this concern is not justified.

In addition to addressing the some of the concerns of the Appraisal Committee, the manufacturer also updated the economic model to:

- consider a lifetime time horizon "to be consistent with previous appraisals in RVO (dexamethasone implant cost effectiveness analysis – TA229)" (Manufacturer's PAS submission; pg 10);
- assume a difference in utility between the best and worst WSE best corrected visual acuity (BCVA) health states of 0.3 "as used in previous submissions – DMO TA237" (manufacturer's PAS submission; pg 10);
- assume excess mortality associated with visual impairment in the WSE (sourced from Christ *et al*.[3], originally implemented by the ERG);
- update adverse event rates associated with ranibizumab and dexamethasone (using data from GENEVA[4] and HORIZON;[5];
- use unpooled transition probabilities in the comparison of ranibizumab with dexamethasone in the BRVO patient population.

The ERG has previously carried out verification of the manufacturer's revised model, in which no errors were identified. Regarding the manufacturer's model revisions, the ERG accepts the:

- adoption of a 90% WSE perspective;
- use and implementation of Brazier utilities;

- assumption of excess mortality associated with visual impairment in the WSE;
- updated adverse event rates.

However, the ERG maintains that the available evidence (Brown *et al.*[6]) suggests a utility decrement of 0.1 (rather than 0.3) between the best and worst WSE BCVA health states. Therefore, the ERG has amended the cost-effectiveness results of the manufacturer's PAS submission to include application of the assumption of a 0.1 utility. The ICERs obtained following the ERG's amendments are presented in Tables 1 to 6.

Table 1. Summary of manufacturer's and ERG's revised BRVO base-case cost-effectiveness results versus GLP (with and without PAS)

Analysis	**Manufacturer's**			**ERG's***		
Treatment	**Ranibizumab**	**Ranibizumab (with PAS)**	**GLP**	**Ranibizumab**	**Ranibizumab (with PAS)**	**GLP**
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (£)	[redacted]	[redacted]	–	[redacted]	[redacted]	–
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALY	[redacted]	[redacted]	–	[redacted]	[redacted]	–
ICER (£/QALY)	**35,068**	**23,073**	–	**67,959**	**44,713**	–

Abbreviations used in table: ERG, Evidence Review Group; GLP, grid laser photocoagulation; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; WSE, worse seeing eye.

*Includes limitation of the maximum benefit of treatment in the WSE to 0.1.

Table 2. Summary of manufacturer's and ERG's revised BRVO cost-effectiveness results versus dexamethasone (with and without PAS)

Analysis	**Manufacturer's**			**ERG's***		
Treatment	**Ranibizumab**	**Ranibizumab (with PAS)**	**Dexamethasone**	**Ranibizumab**	**Ranibizumab (with PAS)**	**Dexamethasone**
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc. costs (£)	[redacted]	[redacted]	–	[redacted]	[redacted]	–
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc. QALY s	[redacted]	[redacted]	–	[redacted]	[redacted]	–
ICER (£/QALY)	**16,664**	**2,370**	–	**28,775**	**4,092**	–

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; WSE, worse seeing eye.

*Includes limitation of the maximum benefit of treatment in the WSE to 0.1.

Table 3. ERG's revised incremental results in BRVO

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus laser (QALYs)	ICER (£) incremental (QALYs)
Without PAS						
Laser	[redacted]	[redacted]	–	–	–	–
Dexamethasone implant	[redacted]	[redacted]	[redacted]	[redacted]	659,750	Extendedly dominated
Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	67,959	67,959
With PAS						
Laser	[redacted]	[redacted]	–	–	–	–
Dexamethasone implant	[redacted]	[redacted]	[redacted]	[redacted]	659,750	Extendedly dominated
Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	44,713	44,713

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

The ERG notes that the revised incremental results in BRVO suggest that dexamethasone is extendedly dominated by ranibizumab (with or without the application of Novartis' PAS) and that, with the application of the manufacturer's PAS, the ICER of ranibizumab versus GLP is £44,713. However, the ERG considers it important to note that there is a considerable amount of uncertainty present in the comparisons of ranibizumab with GLP and with dexamethasone. This uncertainty is a consequence of confounded data from BRAVO (GLP permitted in the ranibizumab arm after 3 months of treatment) used to inform the comparison of ranibizumab with GLP and the absence of a direct comparison of ranibizumab with dexamethasone. Results, of ranibizumab versus dexamethasone, from the manufacturer's revised model are based on the application in month 1 of relative risks (of dexamethasone versus sham injection) derived from an exploratory analysis carried out by the manufacturer. As highlighted in the text following Table 63 of the ERG's original report,[7] the ERG considers that these efficacy estimates may underestimate the efficacy of dexamethasone versus ranibizumab. In addition, the manufacturer's revised model assumes that from month 7 onwards the efficacy of GLP and dexamethasone are equivalent to *pro re nata* (PRN) treatment with ranibizumab. The ERG notes that it remains unclear whether these assumptions would lead to bias towards or against ranibizumab.

Table 4. Summary of manufacturer's and ERG's revised CRVO base-case cost-effectiveness results versus best supportive care (with and without PAS)

Analysis	Manufacturer's			ERG's*		
Treatment	**Ranibizumab**	**Ranibizumab (with PAS)**	**BSC**	**Ranibizumab**	**Ranibizumab (with PAS)**	**BSC**
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALY	[redacted]	[redacted]	–	[redacted]	[redacted]	–
ICER (£/QALY)	**21,796**	**13,851**	–	**41,328**	**26,263**	–

Abbreviations used in table: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; WSE, worse seeing eye.

*Includes limitation of the maximum benefit of treatment in the WSE to 0.1.

Table 5. Summary of manufacturer's and ERG's revised CRVO cost-effectiveness results versus dexamethasone (with and without PAS)

Analysis	Manufacturer's			ERG's*		
Treatment	**Ranibizumab**	**Ranibizumab (with PAS)**	**Dexamethasone**	**Ranibizumab**	**Ranibizumab (with PAS)**	**Dexamethasone**
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc. costs (£)	[redacted]	[redacted]	–	[redacted]	[redacted]	–
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc. QALY	[redacted]	–	–	[redacted]	[redacted]	–
ICER (£/QALY)	**20,155**	**6,995**	–	**35,455**	**12,306**	–

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; WSE, worse seeing eye.

*Includes limitation of the maximum benefit of treatment in the WSE to 0.1.

Table 6. ERG's revised base-case incremental results in CRVO

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus laser (QALYs)	ICER (£) incremental (QALYs)
Without PAS						
BSC	[redacted]	[redacted]	–	–	–	–
Dexamethasone implant	[redacted]	[redacted]	[redacted]	[redacted]	52,583	Extendedly dominated
Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	41,328	41,328
With PAS						
BSC	[redacted]	[redacted]	–	–	–	–
Dexamethasone implant	[redacted]	[redacted]	[redacted]	[redacted]	52,583	Extendedly dominated
Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	26,263	26,263

Abbreviations used in table: BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

The ERG notes that the revised incremental results in CRVO suggest that dexamethasone is extendedly dominated by ranibizumab (with or without the application of Novartis' PAS) and that, with the application of the manufacturer's PAS, the ICER of ranibizumab versus BSC is £26,263. However, the ERG considers it important to note that as a result of the absence of a direct comparison

of ranibizumab with dexamethasone there is a considerable amount of uncertainty present in these results. In particular, the manufacturer assumes that from month 7 onwards, the efficacy of dexamethasone is equivalent to ranibizumab PRN. The ERG notes that it remains unclear whether this assumption would lead to bias towards or against ranibizumab.

Sensitivity analyses

The ERG notes that the manufacturer has carried out deterministic and probabilistic sensitivity analyses for all updated comparisons. However, as a result of time constraints, the ERG has been unable to update these analyses to include a maximum utility gain of 0.1 for treatment in the WSE. However, the ERG notes that the majority of the deterministic sensitivity analyses carried out by the manufacturer affected cost alone; therefore, it is anticipated that the relative impact of these sensitivity analyses on the ERG's revised ICERs would be similar to the impact on the manufacturer's revised ICERs. However, the ERG notes that the manufacturer has included a sensitivity analysis in patients with BRVO incorporating data from HORIZON; the ERG has not been provided with these data and therefore, was unable to validate these analyses.

References

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