National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *BMJ Group* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by ***5pm*, *Monday 25 July 2011*** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29 October 2009

Issue 1 Implications of a prn dosing regimen in HORIZON

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 10, it is stated that the prn dosing regimen of HORIZON may have been insufficient to maintain BCVA in patients with CRVO. It should be made clear that the quarterly follow-up regimen, with prn dosing, is likely to have been the reason for the observed effect in CRVO patients in HORIZON.	Amend to 'quarterly follow-up with the HORIZON PRN dosing regimen may be insufficient'	It is likely to be the frequency of assessment for retreatment, rather the prn criteria perse that is the key issue, although this is uncertain given the small sample size in HORIZON...	No change required. The Summary section represents a summary of the full report and the frequency of follow-up in HORIZON is reported in Box 9 of the ERG report. The ERG considers that this description defines the PRN dosing regimen of HORIZON (ranibizumab 0.5 mg PRN and quarterly follow-up).

Issue 2 Trial design for comparison of ranibizumab versus laser

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 11, it states that for BRAVO to have been a valid comparison of ranibizumab vs. laser, all patients in the control arm would need to have been treated with laser.	'Add sentence 'However, such a comparison would not reflect standard of care or current clinical practice as it would have restricted the population in the study to patients eligible for laser and would not have allowed for patients having spontaneous improvement'.	The limitations of the suggested comparison should be noted, as they are for the suggested comparison of ranibizumab with 'sham only'.	No change required. In the context of the Summary, the ERG has highlighted why it considers the results of the BRAVO RCT to be confounded, and indicated that for a true comparison of ranibizumab against laser or sham injection it considers that patients should be randomised to that treatment alone. Moreover, the ERG considers that grid laser photocoagulation

			is standard treatment for those patients with MO secondary to BRVO who are eligible for laser treatment. The ERG's clinical experts have confirmed that such a comparison would reflect current clinical practice.

Issue 3 Long term treatment effect of laser

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 11, the ERG states that the effects of laser can continue to up to three years after administration.	Add citation details.	The citation details are important in order to assess key study features, including number of treatments, numbers lost to follow-up and clinical outcomes.	No change required. The Summary section represents a summary of the full report and this issue is discussed in more detail in section 4.3.1 of the ERG report with appropriate supporting references.

Issue 4 Interpretation of ranibizumab posology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 13, the ERG states that the SmPC for ranibizumab allows for treatment to be suspended after 3 months when VA is stable, yet the ROCC study suggests that treatment cessation at 3 months may not result in sustained	Remove paragraph	The relevance of this paragraph to the decision problem is unclear, in light of the differences between posology described in the SmPC and the treatment protocol used in the ROCC study.	The ERG agrees that the current text is inaccurate. The text from the point "However, the authors of the ROCC RCT ..." has been deleted and replaced with the

benefit. The posology for ranibizumab allows for treatment suspension only if VA is considered stable and, moreover, allows for treatment to be reinitiated if VA declines. The posology does not imply cessation of treatment at 3 months, as was the case in the ROCC study. It is also noteworthy that the retreatment criteria for the final 3 months of the ROCC study were based on persistence of macular oedema with cysts in the central macular. Conversely, retreatment in the ranibizumab posology is based on visual acuity. The relevance of this paragraph to the decision problem is therefore unclear.			following text: "However, in BRAVO and CRUISE, ranibizumab was administered each month during the treatment phase (0–6 months), even if the patient achieved clinical stability with good BCVA before the 6 month time point (51% in BRAVO ranibizumab 0.5 mg group and 45% in CRUISE ranibizumab 0.5 mg group). Although there are longer term data on the number of injections of ranibizumab given on a PRN basis from the observational phases of BRAVO and CRUISE and the HORIZON extension study, the effects of cessation of ranibizumab injections on visual acuity based on the recommended regimen are unknown."

Issue 5 Relevance of the CATT study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 14, the ERG summarises an outcome of the CATT study comparing bevacizumab and ranibizumab in	Remove the quoted statement from the CATT study	The efficacy of products in wet AMD is not relevant to their efficacy in treating macular oedema secondary to RVO. These are different	No change required. The ERG report presents results from the CATT study to identify what has been

wet AMD and implies this supports their assumption that the two products have equivalent efficacy.		conditions; anti-VEGF therapy in macular oedema acts primarily through preventing vascular leakage rather than preventing both angiogenesis and vascular leakage as in AMD and there are different levels of VEGF expression in the two diseases.	considered a clinically non-significant improvement in BCVA (<5 letters). The ERG notes that using this threshold, the results of its exploratory analysis of ranibizumab versus bevacizumab at 3 months in MO secondary to BRVO suggest that the treatments have similar efficacy at this time point. The ERG does not state in the Summary that the results at 1 year in the CATT study are directly applicable to patients with MO secondary to RVO and thus the results from our exploratory analysis.

Issue 6 Conclusions drawn from the exploratory mixed treatment comparison in BRVO

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 14, the ERG concludes that bevacizumab and ranibizumab may have similar short-term efficacy based on an exploratory MTC at 3 months.	Amend to '...may have similar short-term efficacy...'	No conclusions can be drawn regarding longer term efficacy on the basis of the MTC conducted.	No change required. The summary statement in the ERG report states that the results from the exploratory analysis are based on data at 3 months.

Issue 7 Clarification of the eligible population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 23, the ERG states that no evidence was identified for the incidence of prevalence of MO secondary to RVO.	Amend to '...no evidence was found for the incidence and prevalence of visual impairment due to MO secondary to RVO.' Or 'no evidence was found for the incidence and prevalence of MO secondary to RVO specific to England and Wales.'	To accurately represent the data identified and available.	The ERG agrees that the current text is inaccurate. The words "visual impairment" have been added as suggested by the manufacturer.
On page 23 and 24, the proportion of patients developing MO due to RVO is cited from a systematic review. This proportion does not take account of the number of patients with MO at baseline (as measured by OCT) reported in the primary citation.	Amend to 'However, in BRVO, Rogers *et al.* suggest that, over a 1-year period amongst those without MO at diagnosis, 5% to 15% of eyes develop MO'	To contextualise the eligible population.	No change required. The sentence in the ERG report reads: "However, in BRVO, Rogers *et al*.[10] suggest that, over a 1-year period, 5% to 15% of eyes develop MO." The ERG notes that if eyes develop MO they do not have MO at baseline.

Issue 8 Inclusion of bevacizumab as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 30, the ERG notes that the RCO guidelines state bevacizumab is used extensively in clinical practice but omits the	'..used extensively...for the management of many retinal conditions that have a VEGF driven pathophysiology.'	Use of a product across retinal conditions does not provide evidence of routine use or best	No change required. The ERG considers that since MO secondary to RVO has a

subsequent statement also presented in the RCO guidelines ('for the management of many retinal conditions that have a VEGF driven pathophysiology')		practice in MO secondary to RVO.	VEGF-driven pathophysiology it is appropriate to interpret the statement made in the RCO guidelines as meaning bevacizumab is used in the treatment of MO secondary to RVO.
On page 111, the ERG uses the statement in the RCO guidelines to imply that bevacizumab is routinely used to treat MO due to RVO. This conclusion cannot be drawn from the RCO guidelines	Removal of this sentence.	Use of a product across retinal conditions does not provide evidence of routine use or best practice in MO secondary to RVO.	
On page 111, the ERG notes that the ERG for ranibizumab in DMO appraisal concluded that bevacizumab was used sufficiently in DMO to warrant comparison. The use of therapies in DMO is not relevant to the decision about comparators for ranibizumab in RVO.	Removal of this sentence.	Use of a produce in other retinal conditions does not provide evidence of routine use or best practice in MO secondary to RVO.	No change required. The ERG considers that therapies used in one VEGF-driven condition would be used in other VEGF-driven conditions.

Issue 9 Definition of resolution

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 44, the ERG states that the proportion of sham patients in BRAVO with an improvement of 15 or more letters from baseline score at month 3 is comparable to published estimates of the proportion of patients showing resolution. This suggests that a	Removal of the sentence beginning 'These data are in accordance with the rates...'.	The suggested definition of spontaneous resolution is not accurate	The ERG agrees that the current text is inaccurate. The sentence highlighted by the manufacturer has been replaced with the following text: These data suggest that there could be benefit in delaying

15 letter improvement in BCVA is equivalent to a resolution of MO due to RVO, which is not a standard definition and is unlikely to be equivalent to resolution for many patients.			treatment to allow for spontaneous improvement.

Issue 10 Tables throughout presenting data to 12 months of BRAVO and CRUISE

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the ERG report the control arm of BRAVO and CRUISE is described as sham. In fact, because all patients could receive ranibizumab from month 6-12, where outcomes at 12 months are presented the control arms could be labelled sham/0.5 mg ranibizumab for greater clarity.	Amend 'sham' to 'sham/0.5 mg ranibizumab' in all tables presenting outcomes after 6 months.	Greater accuracy and clarity	The ERG agrees that the current text is inaccurate. The ERG identified three tables to which this comment applied and that have not been mentioned in another issue (Tables 5, 7, and 8). The label of the sham column in the tables has been amended to "sham/0.5 mg" as in other tables in the ERG report.

Issue 11 Evidence for safety of bevacizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 55 the ERG states that retrospective studies of safety outcomes in a wet AMD population may not be applicable to an RVO population. This is inconsistent with the previous implication in the report that results of the CATT study are applicable to efficacy in an RVO population. Further this does not take into account that issues of systemic safety may be expected to be applicable across indications, notwithstanding baseline differences between patient populations.	Removal of the statement described in issue 5.	Consistency between previous statements.	No change required. The ERG considers that direct comparisons among different conditions with regards to the adverse effects of a drug cannot be made and the statement made is accurate. Regarding issue 5, as previously commented, the ERG does not consider that it has stated that the efficacy results from the CATT study are directly applicable to an RVO population Please see the ERG's response to issue 5 for further details.

Issue 12 Description of rationale for inclusion of bevacizumab as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 61, the ERG states that since bevacizumab is used throughout the NHS to treat ocular conditions, albeit infrequently, it is a valid comparator. The conclusion that it is a valid comparator is not in line with the NICE guide to the	Removal of the sentence beginning 'This aligns with.....'.	The statement is inaccurate.	No change required. On pg 61, the sentence referred to by the manufacturer is affirming that the ERG considers its opinion that bevacizumab is used in the NHS (albeit unlicensed usage)

methods of technology appraisal. Furthermore, the RCO guidelines conclude that they can make no recommendation regarding the use of bevacizumab in RVO. The clinical specialists who presented their view to the Appraisal Committee for dexamethasone referred to the RCO guidelines as well as the GMC guidance for prescribing unlicensed drugs, when a licensed alternative is available. It is inaccurate to state that the RCO guidelines or the clinical specialists for a different appraisal concluded that bevacizumab is an appropriate comparator for ranibizumab.			to treat ocular conditions with VEGF-driven pathophysiology is in alignment with comments in the RCO guidelines and those made by clinical specialists attending the appraisal committee meeting on dexamethasone intravitreal implant for MO secondary to RVO.

Issue 13 Conclusions regarding potential bias in indirect comparison due to presence of ischaemic patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 63, the ERG refers to the proportion of patients in the GENEVA study that developed neovascularisation in the GENEVA study. The ERG concludes that the presence of ischaemic patients in GENEVA may have led to an underestimation of treatment effect and therefore bias towards ranibizumab in an indirect comparison. The ERG has overlooked data from BRAVO and	Removal of the conclusion that there may be bias towards ranibizumab in any indirect comparison.	The conclusion drawn appears to be inaccurate.	No change required. The ERG agrees with the manufacturer that people in the sham groups of BRAVO and CRUISE developed neovascularisation. However, on page 63, the ERG highlights that the number of people with ischaemia in GENEVA is uncertain as GENEVA reports that

CRUISE which suggests similar proportions of neovascularisation.			presence of ischaemia was not assessed at baseline. Whereas, in the manufacturer's submission, the manufacturer indicates that presence of ischaemia at baseline was assessed and patients classified as ischaemic based on the criteria of presence of >10 disc areas of capillary non-perfusion. The manufacturer reports that 0 people in BRAVO and 2 people in CRUISE had ischaemic disease. The ERG considers that it is unknown how many people had ischaemic disease in GENEVA and that its comment highlights that should there be a larger proportion of people with ischaemia in GENEVA then this would favour ranibizumab in an indirect comparison.

Issue 14 Description of eligible population in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81, the ERG states that 'all CRVO and BRVO patients are eligible for ranibizumab'. In fact, only patients with visual impairment due to MO secondary to BRVO or CRVO are eligible for ranibizumab treatment and are therefore entered into the model.	Add '...all patients with visual impairment due to MO secondary to CRVO and BRVO are eligible for ranibizumab.'	Greater clarity regarding the eligible population	No change required. The ERG has used a shortened description of the indication, which may be understood in the context of the paragraph.

Issue 15 Description of costing assumptions for laser

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 92, the ERG states that there are no direct treatment costs for laser. It would be more accurate to clarify that this is an assumption of the analysis. That is, that capital costs and costs of maintenance are excluded from the analysis.	Revise to '..the model assumes no direct treatment costs for GLP...'	The statement is inaccurate.	The ERG agrees that the current text is inaccurate. The sentence has been amended to "the manufacturer assumes no direct treatment costs for GLP".

Issue 16 Application of costs of blindness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 93, the ERG states that the costs of blindness were applied only to the first year of blindness. In fact, this should read the costs of low vision aids and low vision rehabilitation were only applied to the first year of blindness to accurately reflect the manufacturer's submission.	Clarify that subsequent annual costs of blindness are included in the model, but exclude the cost of items considered as one-off costs in previous NICE appraisals of eye conditions.	Accurate representation of the manufacturer's model and submission.	The ERG agrees that the current text is inaccurate. The sentence has been amended to "The MS states that the costs of low vision aids and low vision rehabilitation were only applied in the first year of blindness". Also to accurately report that a cost of blindness is applied annually, the sentence in the previous paragraph "The costs of blindness were drawn from Colquitt *et al*. and applied using the same methodology as that used by the ERG responsible for reviewing Allergan's submission to NICE for dexamethasone intravitreal implant in MO secondary to RVO" has been updated to include the word annually.

Issue 17 Description of Brazier utilities and TA155

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 104, 105 and 108, the	Amend to 'the manufacturer did not use the	To add clarity regarding the status	pg 104/108. No change

ERG notes that the manufacturer did not use the recommended source of utilities from TA155. Although Novartis agrees with the TA155 Appraisal Committee's conclusion regarding the limitations of generic measures of utilities in capturing the impact of vision loss, and the advantages of the Brazier utilities, it is not clear that the Committee recommended these utilities for use in all ocular conditions.	source of utilities preferred by the Committee in TA155'.	of the Brazier utilities	required. The Brazier utilities were "recommended" by the appraisal committee in TA155. Therefore these statements are correct. pg 105. The ERG agrees that the current text is inaccurate. The appraisal committee for TA155 did not recommend the Brazier utilities for use in all ocular conditions. The words "for ocular conditions" have been removed.
The utilities presented in table 53 (page 108), and reproduced from the paper by Czoski-Murray et al (citation 40 in the ERG report), differ to those used in TA155. The utilities derived for inclusion in the TA155 model included values across 5 BCVA health states of the wet AMD model. Furthermore, the application of the published utilities may not be accurate given that no account has been taken of the regression equation proposed by Czoski-Murray et al.	The limitations of the analysis incorporating utilities from the Czoski-Murray at el paper should be included in the ERG report.	The ERGs additional analysis does not appear to reflect the preference of the TA155 Appraisal Committee, and the limitations of their approach should be noted.	No change required. The ERG did not have access to the utility values used in TA155 and conducted the scenario analysis based only on information from the Czoski-Murray paper. The main limitation of this analysis (lack of model calibration) is stated previously (pg 106 of the ERG report).
On page 108, the ERG report states that clinical experts to the manufacturer concluded that the utility associated with visual acuity	Reference to the manufacturer's clinical experts should be removed.	The statement is inaccurate.	The ERG agrees that the current text is inaccurate.

is applicable across vision disorders. This conclusion is not presented in the manufacturer's submission.			The manufacturer supplied a summary of the views expressed by their clinical experts in Appendix 21, the ERG notes that the clinical experts views on the impact of visual impairment caused by different diseases on health related quality of life is absent. However, on page 226 of the MS, the manufacturer states that "the clinical experts concluded that age and extent of affected eyes were important in determining whether utilities were applicable across vision disorders." As the underlying condition was not listed as important, the ERG has interpreted this to concur that utility is more dependent on visual impairment than on the underlying ocular disease itself. The ERG notes that the MS also states that "The clinical experts also highlighted that the extent of loss of the visual field versus central vision loss is different between ocular diseases". The sentence has been amended to "expert clinical opinion from both the

			manufacturer and the ERG concur that the utility associated with visual acuity may be applicable across vision disorders".

Issue 18 Description of available evidence for risk of other ocular conditions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 107, the ERG states that it is unaware of any evidence suggesting that patients with RVO are at higher risk of developing ocular conditions compared with the general population. Whilst this statement may not be inaccurate, we would highlight page 11 of the RCO guidelines which summarises potential associations of RVO to diabetes mellitus and glaucoma (evidence levels B and C respectively). Patients with diabetes are more likely to develop ocular complications than the general population.	Removal of this sentence or addition of evidence as summarised in the RCO guidelines.	The statement is incomplete.	No change required. The ERG has not seen any evidence suggesting that patients with RVO have an increased risk of developing ocular conditions compared with the general population.

Issue 19 Description of additional analysis using unpooled transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 113, the ERG concludes that applying the unpooled transition probabilities (TPs) from 7-12 months of BRAVO to the cost effectiveness analysis demonstrates that the using the pooled 7-12 month TPs inflates the effect of ranibizumab. The report does not makes clear that the sham arm is in fact the sham/0.5 mg arm of BRAVO (see also issue 9) and represents patients receiving ranibizumab for the first time where the efficacy outcome would be expected to be most marked. Table 57 is therefore somewhat misleading.	Amend table 57 and describe limitations of the analysis	The presentation of this analysis is inaccurate and therefore misleading	The ERG agrees that the column heading in Table 57 is inaccurate. The label of the sham column has been amended to "sham/0.5 mg" as in other tables in the ERG report. However, the ERG has not changed the wording of the text. The surrounding text contextualises the information in Table 57. The manufacturer has not specified any limitations of this analysis.

Issue 20 Availability of patient level data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 116, the ERG notes that it did not have access to the individual patient data (IPD) from CRUISE to generate additional transition probabilities. The IPD was provided, and again in alternative software at the request	Remove statement.	The statement is inaccurate.	The ERG agrees that the current text is inaccurate. The ERG discusses the provision of IPD data in the ERG report (pg 112). In summary, the manufacturer

of the ERG. NICE acknowledged receipt of the data on both occasions.			initially provided IPD data in SAS, which is not a preferred NICE format. The manufacturer subsequently provided the data in EXCEL. The absence of an accompanying key meant that the ERG could not interpret the data during the drafting of the report. The statement on page 116 has been amended to "However, the absence of an explanatory key for the IPD submitted by the manufacturer, along with the late arrival of this data, meant the ERG was unable to formulate the month 7 to 12 transition probabilities for the sham arm required to permit this analysis".

Issue 21 Conclusions regarding the structure of the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 105 and 106, the ERG suggests that a model with fewer health states would be more appropriate and that the model structure used may overestimate	The basis for the ERG's concern should be noted in the report.	The conclusions regarding the model structure are speculative and do not present the alternative possibility, and are therefore incomplete.	No change required. The basis of the ERG's concern is that health benefits may be over-estimated, a natural result of unnecessary

the benefits of ranibizumab. There is no clarification as to the basis of this concern, or the rationale for the perceived direction of bias.			additional granularity in health states. The direction of bias is apparent by the increase in the ICER when fewer health states are used.
On page 106, the ERG concludes that the ICERs generated by applying the four published 'Brazier' utilities to the model support their theory that the model overestimates the benefit. As noted by the ERG their revised analysis did not include revising the IPD and is therefore exploratory.	The limitations of the inclusion of the Brazier utilities should be explicitly noted.	The conclusions are speculative and incomplete.	No change required. The ERG has not drawn any conclusions, as it is not possible to do so without full model recalibration. The report clearly states the limitation of this analysis and that the supposition cannot be confirmed.

Issue 22 Description of limitations of the data to parameterise the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 132, the ERG states that data from the BVO Study could not be implemented in the model because of its structure. The ERG report does not include the difficulties arising from the limited published outcomes from BVOS.	Addition of a description of the difficulties in including limited published evidence in the model.	The conclusions regarding the difficulties in including BVO Study data in a model are incomplete.	No change required. It is beyond the remit of the ERG to discuss the way in which the model would need to be structured (and the difficulties associated with that) in order to accommodate data from BVOS.

Issue 23 Description of need for further research for ranibizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 135, the ERG states 'there is a need for further research into the safety and clinical benefit of ranibizumab compared with all treatments currently used in clinical practice'. This suggests a limitation of the safety and efficacy data for ranibizumab, which is extensive – particularly in comparison to other treatments.	Amend to 'there is a need for further research into the safety and clinical benefit of other treatments for visual impairment due to MO secondary to RVO, to enable a full comparison to ranibizumab'	The statement is incomplete.	The ERG agrees that the current text is inaccurate. The sentence has been amended to: The ERG considers that there is a need for further research into the safety and clinical benefit of ranibizumab compared with other treatments currently used in clinical practice for treatment of visual impairment due to MO secondary to RVO.

Further erratum

These errors were identified by the ERG after the report had been sent for consultation.

Section 6.1.1, pg 122. The ICERs for scenario J and K in Table 67 were incorrectly entered as £19,868 and £21,922 and have been amended to £46,760 and £68,827 respectively.

Section 7, pg 133. The sentence, "However, the presence of conflicting bias makes it difficult to say with certainty which treatment is favoured in the manufacturer's approach" has been deleted.