6 June 2011

National Institute for Health and Clinical Excellence

NICE
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

Tel: 0161 870 3152
Fax: 0207 061 9764

Email: [redacted]

www.nice.org.uk

Dear [redacted]

Single Technology Appraisal

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

The Evidence Review Group (BMJ-Technology Assessment Group) and the technical team at NICE have now had an opportunity to take a look at submission received on 10 May 2011 from Novartis Pharmaceuticals for this appraisal. The ERG and the NICE technical team have identified some areas relating to the clinical and cost-effectiveness on which we would like further clarification.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Friday 17 June 2011**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not ‘embed’ documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted] – [redacted]. Any procedural questions should be addressed to [redacted] – [redacted] in the first instance.

Yours sincerely

[redacted]

[redacted]

Centre for Health Technology Evaluation

Encl. checklist for in confidence information

SECTION A – Clarifications of the clinical data:

A1. The submission lists two exploratory outcomes that are not listed in the Clinical Study Reports for BRAVO and CRUISE: (i) the proportion of patients who gained ≥ 10 letters at 6 months; and (ii) the proportion of patients who lost ≥ 10 letters at 6 months. Please confirm that these are post-hoc analyses?

A2. The pre-specified primary outcome listed in BRAVO and CRUISE is mean change from baseline BCVA at month 6, with percentage of patients who gained 15 or more letters at month 6 listed as a secondary outcome. Please comment on why "the proportion of patients with an improvement in best corrected visual acuity, as measured by an improvement from baseline to six months of 10 or more letters read on an Early Treatment Diabetic Retinopathy Study Chart at four metres, equivalent to 0.2 logMAR" (page 48) has been chosen as the primary outcome for the systematic review of the literature.

A3. For the BRAVO RCT, how many people in the sham group had oedema that spontaneously resolved at 3 months (based on a visual acuity of ≥20/40 and OCT <250 microns)?

A4. For the BRAVO RCT, please populate the grid below to indicate the mean change in best-corrected visual acuity (BCVA) in the sham group at the time points listed and the number of people who achieved the specified levels of improvement in visual acuity.

Table 1: Visual acuity outcomes in the sham group up to 3 months.

BRAVO	**Month 1**	**Month 2**	**Month 3**
Mean change in BCVA from baseline			
Number of patients achieving an improvement of ≥ 15 letters			
Number of patients achieving an improvement of ≥ 10 letters			

A5. For the BRAVO RCT, please populate the grid below to indicate the mean change in BCVA at the time points listed and the number of people in the ranibizumab 0.5 mg group who achieved specified levels of improvement in visual acuity (percentages are given in the manufacturer's submission).

Table 2: Patient visual acuity outcomes for the ranibizumab 0.5 mg group up to 3 months.

	Month 1	**Month 2**	**Month 3**
Mean change in BCVA from baseline			
Number of patients achieving an improvement of ≥ 15 letters			
Number of patients achieving an improvement of ≥ 10 letters			

A6. For all those patients in BRAVO who received laser treatment **within the 6 month treatment period**, please populate the table below.

	Sham group	**0.5 mg ranibizumab group**
Last observation prior to laser treatment for those patients receiving laser treatment by month 6		
Number of people being assessed		
Mean visual acuity		
Mean change in BCVA from baseline		
Number of patients gaining ≥15 letters		
Number of patients gaining ≥10 letters		
Outcomes measures at 6 months for those patients who received laser treatment by month 6		
Number of people being assessed		
Mean visual acuity		
Mean change in BCVA from baseline		

Number of patients gaining ≥15 letters		
Number of patients gaining ≥10 letters		
Outcomes measures at 12 months for those patients who received laser treatment by month 6		
Number of people being assessed		
Mean visual acuity		
Mean change in BCVA from baseline		
Number of patients gaining ≥15 letters		
Number of patients gaining ≥10 letters		

A7. In accordance with the NICE final scope and the NICE Methods Guide, using available data and providing an account of any potential bias, please provide comparisons between:

i. ranibizumab versus dexamethasone for BRVO and CRVO;
ii. ranibizumab versus bevacizumab in BRVO and CRVO;
iii. ranibizumab versus grid pattern photocoagulation in BRVO (as opposed to sham followed by rescue laser).

A8. The exclusion criteria for BRAVO and CRUISE indicate that people with prior episodes of RVO were excluded from the trials, yet tables B7 and B8 indicate that [redacted] people in BRAVO and CRUISE, respectively, had prior therapy for RVO in the study eye. Please comment on the cause of this apparent discrepancy.

A9. Please supply full details for the search terms and search strategies, and the databases and resources searched to identify non-RCT data for bevacizumab (discussed in Appendix 20 [page 380]).

A10. Please clarify whether the criteria applied for treatment for those continuing from BRAVO into HORIZON (given in table B5, page 64) were also applied to those enrolling in HORIZON from the CRUISE RCT (not listed in table B5, page 64).

A11. Please clarify whether presence of macular ischaemia was assessed in people entering BRAVO and CRUISE?

SECTION B – Clarifications of the economic data

B1 Priority question. Please provide individual patient level data so that the ERG can validate the transition probabilities presented in the model.

B2 Priority question. Within the model on the sheet entitled "Nice Outputs", there is a table (D188:O222) describing the data availability of each subgroup per treatment. This table states that data are available for Bevacizumab in all BRVO patients. The ERG group requests details of these data and the results of any analyses performed on these data.

B3 Priority question. Please provide a scenario analysis in which the model uses the pre-specified trial outcome of a gain/loss of ≥ 15 letters rather than the analysis of 10 or more letters.

B4. Please provide the unpooled 7 to 12 month transition probability matrices of the ranibizumab and sham arms in BRAVO.

B5. Please provide full calculation details of the incorporation of dexamethasone into the model, indicating which values were taken from the Haller 2010 paper, how they were manipulated and applied to the model.

B6. Please provide the following summaries:

i. Tabular comparisons of the following trial results:
    a. Proportion of patients gaining 15 letters
    b. Proportion of patients losing 15 letters
    c. Proportion of patients gaining 10 letters
    d. Proportion of patients losing 10 letters

versus those obtained from the model for all BRVO and all CRVO patients at 3, 6 and 12 months

ii. Tornado plots of all deterministic sensitivity analysis;
iii. A complete summary table of all model parameters;
iv. Plots of all Markov traces.

B7. The ERG requests an updated model that includes age adjusted utilities.

B8. Please clarify the rationale for including stroke in the economic model, when there is no difference in incidence between treatment arms.

B9. Brazier 2009 has been approved in TA155 as the best source of visual acuity related utility. Please provide further information as to why the visual acuity utility data from Brazier 2009, which was used in TA155, has not been used to inform health state utilities.

B10. Please provide a detailed description with a worked example of where the probability manipulation method described on page 245 of the submission is used in the model.

B11. Please clarify why the administration cost of laser therapy used in the model (£110.59) differs from that reported on page 235 of the submission (£192).

B12. Page 248 of the submission states that there are slight differences between the BCVA of the trials and the model. Please explain why this is the case.

B13. Please clarify why the number of follow up visits for 3+ years used in the model (4), differs from that reported in the submission on pages 192 and 237 (2).

B14. In section C of the submission, table C1 reports that 50% of BRVO patients experience visual impairment. Please clarify how this number was used in the calculation of the number of patients with visual impairment due to MO secondary to BRVO.

B15. When fellow eye involvement (FEI) is considered in the model, the different methods of drug cost calculations used before and after the assumed maximum treatment duration suggests that the drug costs may be underestimated. Patients experiencing FEI at, for example 23 months, have the cost of only one treatment applied, whereas patients experiencing FEI after the assumed maximum duration of treatment have the full 2 year cost of treatment in the fellow eye applied. Please confirm if this is an error. Please also correct this error so that all patients who experience FEI have the full cost of treatment applied.