21 October 2010

NHS
National Institute for Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Tel: 0161 870 3152
Fax: 020 7061 9764

Email: lori.farrar@nice.org.uk

www.nice.org.uk

Dear [redacted],

Re: Single Technology Appraisal – **dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion**

The Evidence Review Group at the University of Aberdeen and the technical team at NICE have now had an opportunity to take a look at submission received on the 27th September 2010 by Allergan. The ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

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 **17:00, 4 November 2010**. 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 '[redacted]' in turquoise, and all information submitted under '[redacted]' 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 Jennifer Priaulx – Technical Lead (jennifer.priaulx@nice.org.uk) Any

procedural questions should be addressed to Lori Farrar – Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. Please can you provide the clinical trial reports for the GENEVA 008 and 009 studies and indicate on the checklist the confidentiality status of the information contained in the reports?

A2. (Page 53, table 19.) Is there any variation in the volume of dexamethasone released from the implant over the course of 180 days (i.e. are there peaks rather than a steady release)? If so, please comment on how this variation may relate to the results in visual acuity at each time point (30, 60, 90, 180 days).

A3. The GENEVA trials involved treatment with a dexamethasone intravitreal implant at baseline, then no further retreatment until 180 days. In routine care, there would be more flexibility of dosing. Have you modelled a repeat dose in CRVO as soon as visual acuity starts to decline? If so, please describe the method, results and any assumptions made about efficacy of the second dose.

A4. (Page 21) Please provide a copy of the evaluation of the three most commonly used therapeutic interventions (laser photocoagulation, off-label use of VEGF inhibitors and corticosteroids) that was provided to the European Medicines Agency.

A5. (Page 30, reference number 25.) The Haller paper mentions that some patients had "prohibited" interventions. Please clarify what these interventions were and the reason(s) why they were given.

A6. (Pages 30-31 and 88-89.) Section 5.7 states that no indirect comparison could be conducted between bevacizumab or triamcinolone acetonide and dexamethasone intravitreal implant owing to absence of appropriate RCT evidence found in the systematic review. Please clarify whether studies of bevacizumab and triamcinolone were identified but excluded from the systematic review and, if so, provide details of these studies.

A7. (Page 25.) It is suggested that Trevaris will not be available in UK. Please clarify the source of this information.

A8. (Page 47, table 14.) Please can you provide any further information to explain why there were only a few drop-outs due to lack of efficacy in the sham group?

A9. (Page 54-55, tables 20, 22, 23.) It appears that the branch retinal vein occlusion (BRVO) macular haemorrhage (MH) and previous laser groups do better than the total BRVO group. Please can you comment on why this might be the case?

A10. (Page 61-62, table 28 and 29.) Please provide the percentage distribution of visual acuity at each time point for CRVO and BRVO separately (as in table 27) or clarify that these data are not available.

A11. (Page 69, paragraph 2.) Please provide the same data on the effect of delayed treatment on primary outcome for CRVO and BRVO separately.

A12. (Page 90-117.) The maximum number of doses is six doses. Do you have data on eye complications after 5-6 injections using a 22-gauge needle?

A13. (Page 139-145.) In order to better understand the patient flow within the GENEVA studies, please tabulate the following absolute patient numbers where the total for day 180 and day 360 should remain as the overall modified intent-to-treat (mITT) population of the group under consideration at day 0, where the data is available for the dexamethasone intravitreal implant arm:

DEXAMETHASONE	CRVO All			BRVO All			BRVO ME<=90dy			BRVO ME>90dy		
Day	0	180	360	0	180	360	0	180	360	0	180	360
Treated with dexamethasone												
Not treated with dexamethasone due to												
Macular oedema (ME) resolved	..			..			..			..		
Safety	..			..			..			..		
Other	..			..			..			..		
Lost to Follow Up	..			..			..			..		
Not part of open label protocol	..	..		..	..		..	..		..	..	
Total												

Please also present a similar data set for the sham arm:

SHAM	CRVO All			BRVO All			BRVO ME<=90dy			BRVO ME>90dy		
Day	0	180	360	0	180	360	0	180	360	0	180	360
Treated with dexamethasone	..			..			..			..		
Not treated with dexamethasone due to												
Macular oedema (ME) resolved	..			..			..			..		
Safety	..			..			..			..		
Other	..			..			..			..		
Lost to Follow Up	..			..			..			..		
Not part of open label protocol	..	..		..	..		..	..		..	.	
Total												

Section B: Clarification on cost-effectiveness data

B1. (Page 139-145.) Please clarify which patient population within the dexamethasone intravitreal implant arm was used to calculate the day 0-30, day 30-60, day 60-90 and day 90-180 transition probability matrices (for example, the 421 patients receiving a dexamethasone injection at baseline; the 401 patients receiving an injection at baseline and entered the open label phase; the 341 patients receiving an injection at both baseline and day 180).

B2. Please also clarify which population within the dexamethasone intravitreal implant arm was used to calculate the day 180-360 transition probability matrices (for example, the 341 patients receiving a dexamethasone injection at both baseline and day 180; the 341 patients receiving a dexamethasone injection at both baseline and day 180 plus the 327 patients receiving a sham injection at baseline and a dexamethasone injection at day 180).

B3. Please clarify which patient population within the sham treatment arm was used to calculate the transition probability matrices (for example, the 423 patients receiving a sham injection at baseline; the 399 patients receiving an injection at baseline and entered the open label phase; the 327 patients receiving an injection at baseline and a dexamethasone injection at day 180).

B4. (Page 139-145) There are a number of distinct transition probability matrices for CRVO, BRVO, BRVO with MH, BRVO with previous laser and BRVO of more than and 90 days or less within the electronic model. Please can you present the results from applying the distinct baseline distributions of each group rather than the pooled distribution across all subgroup analyses?

B5. (Page 86, 132, 141, 165 and elsewhere.) The clinical trial evidence suggests that the majority of patients needed re-treatment but there is currently no data on how many doses will be used in clinical practice. To address this uncertainty, please provide another scenario analysis (table 115) at two years with three injections.

B6. (Page 145-146 and 151-154.) From the text, it appears that values for the split of best seeing eye (BSE) and worst seeing eye (WSE), time to stabilisation of best corrected visual acuity (BCVA) [incl. natural history] and retreatment rates were taken from the panel held in New York on 30 September 2009. Please clarify to what extent the other panels on 12 November 2009, 12 May 2010 and other expert opinion contributed data on these aspects:

	30 Sep 2009	Nov 12 2009	May 12 2009	Other
BSE:WSE split	Contributed	[please insert]	Contributed	[please insert]
Time to stabilisation of BCVA	Contributed	[please insert]	[please insert]	[please insert]
Retreatment rates	Contributed	[please insert]	[please insert]	[please insert]

i. Where there were contributions from more than one panel, to what extent were the consensuses reached through discussion the same across the contributing panels?

ii. Please verify the BSE: WSE 90:10 ratio on page 151

iii. Please clarify the extent to which information from the New York clinical expert panel was focused on the UK context.

B7. (Page 151-152.) For the base case the proportions retreated and not retreated with a 2nd injection at day 180 are described as taken from the pooled trial data. The proportions treated and not retreated with a 3rd injection and beyond are drawn from the New York expert panel. From the trial data please present a disaggregate analysis of the numbers of dexamethasone intravitreal implant patients retreated at day 180 disaggregated by health state: HS0, HS1, HS2, HS3, HS4 and HS5.

B8. (Page 153.) Within the model, those patients who are not retreated are assumed to have either resolved or to have dropped out. Those having resolved have the identity matrix applied to them, while those who have dropped out have the sham matrix applied to them. The proportions of those not being treated who resolve are taken from trial data. Please clarify:

i. At what time point resolution was evaluated (e.g. day 180).

ii. Whether any proportion of those assessed as resolved within the trial at day 180, and so contributing to the resolution estimates, received a second injection, split by CRVO and BRVO.

B9. The patients estimated to have resolved within the model are given as percentages (shown below). Please clarify the absolute numbers of patients that the percentages of relate to, giving the numerator and the denominator.

	HS0	HS1	HS2	HS3	HS4	HS5
CRVO						
BRVO						

B10. (Page 160-161, section 6.4.9.) In terms of how the patient utility for a given health state is calculated, please clarify:

i. If only the WSE is affected and the patient is in HS2, is the utility value [redacted]?

ii. If only the BSE is affected and the patient is in HS2, is the utility value [redacted]?

iii. If the WSE is affected initially and is currently in HS2, with fellow eye involvement in the BSE with the BSE currently being in HS2 is the utility value [redacted]?

B11. (Page 160-161.) Please present the standard errors of the intercept and slope parameters within the two utility regression equations.

B12. (Page 160-161.) In terms of estimating the utility regressions was this undertaken for any particular time point within the trial, or was data pooled across different time points used?

B13. (Page 165, paragraph 3.) Please provide any evidence of whether monitoring of visual acuity with a view to earlier re-treatment would increase the number of visits required or whether it would condense the same number of visits into a shorter time period.

B14. (Pages 177 and 180.) Please verify that the proportion of patients with the two best health states is similar between treated CRVO and observed CRVO.

B15. (Page 181, tables 124-127.) Please clarify how the data for life years have been calculated.

Electronic model

B16. In checking the results for BRVO with MH, setting D32 equal to 4 the results for BRVO do change to those of the submission: £7953 per QALY. But this also changes the CRVO cost effectiveness to £5,803 per QALY. There is no obvious reason why the cost effectiveness for CRVO should change and this suggests there may be some error in the coding of the model. Please clarify if this is the case, and any changes necessary to correct the model structure.

B17. As a face validity check, please consider the following:

	100% RVO to ME conversion			50% RVO to ME conversion		
	All RVO	CRVO	BRVO	All RVO	CRVO	BRVO
Discounted		All	All		All	All
Ozurdex						
Cost	£12,245	£14,962	£10,815	£10,567	£13,363	£9,095
QALY	11.6916	11.6246	11.7269	11.6350	11.5638	11.6725
No treatment						
Cost	£10,578	£13,126	£9,236	£7,873	£10,432	£6,526
QALY	11.465	11.319	11.5424	11.449	11.295	11.5307
Ozurdex-no treatment						
Cost	£1,667	£1,836	£1,578	£2,694	£2,931	£2,569
QALY	0.23	0.31	0.18	0.19	0.27	0.14
ICER	**£7,368**	**£6,008**	**£8,554**	**£14,502**	**£10,884**	**£18,119**

The average total QALYs fall if the proportion of RVO resulting in ME is reduced from 100% to 50%, and falls further if the proportion is reduced to 0%. Similar effects appear to be the case if the method of modelling fellow eye involvement is changed to a simple rate calculation: a lower rate of fellow eye involvement worsens the aggregate patient QALYs. This seems counterintuitive and may suggest a logical flaw in the model structure, which if the case, could have a major impact given the importance of fellow eye involvement to the cost effectiveness argument. Please clarify if this is the case, and any changes necessary to correct the model structure.

B18. Within the 'Transitions' worksheet it appears that the transition probability matrices for those in the dexamethasone arm not treated, rows 63:75, rely upon the two matrices in columns CN:CZ when the assumption is that they are a weighted average of the identity matrix and the SHAM2 matrix D90-D180. Relying upon the two matrices in columns CN:CZ appears to suggest that these transition probability matrices are invariant through time. There might be some concerns around this if the assumptions for dexamethasone

and sham transition probability matrices subsequent to D180 are not as per the base case assumptions; e.g. decay is assumed for these. Please clarify if this is the case.

B19. The ERG has attempted to reconstruct the cohort flow of the model as a cross check to that submitted. Given time constraints, this has not been cross checked and the ERG does not suggest that this accurately models the decision problem. The ERG modelled BRVO cohort flow is a simple copy of the ERG modelled CRVO cohort flow with Search and Replace of some text, as outlined in the Comments worksheet.

Within the ERG Cross Check mortality is not modelled within the cohort flow, but is rather applied at the final summation as a conditioner on the accrued QALY within the relevant cycle, much like the application of the discount rate. As such, as a simplification the ERG Cross check does not currently implement a mortality multiplier for blindness. The cohort flow should broadly correspond to that of the submitted model if within the submitted model; the mortality multiplier for blindness is set equal to 1; the retreatment proportions as set equal to 1; and, the cycle hazards of death are set equal to 0.

Steady state from cycle 10		HS0	HS1	HS2	HS3	HS4	HS5
ERG Cross Check	CRVO DEXA	[redacted]					
Adj. Submission	CRVO DEXA	[redacted]					
ERG Cross Check	CRVO SHAM	[redacted]					
Adj. Submission	CRVO SHAM	[redacted]					
ERG Cross Check	BRVO DEXA	[redacted]					
Adj. Submission	BRVO DEXA	[redacted]					
ERG Cross Check	BRVO SHAM	[redacted]					
Adj. Submission	BRVO SHAM	[redacted]					

Given this there seems to be reasonable correspondence between the ERG Cross Check and the submitted model in terms of the main cohort flow. Matters become more complicated in terms of the modelling of fellow eye involvement. Given the concerns around the impact of changing the rate of fellow eye involvement on total QALYs as outlined above this is a particularly important aspect of the model to understand.

This aspect of the submitted model is particularly difficult to follow and some account of the logical structure of the modelling of this aspect would be much appreciated. It is appreciated that this is not a trivial description, and as a consequence the simplest description would explain the logic and associations between and resulting calculations underlying:

- the mortality adjusted incidence of cells CG17:DJ17 and the no fellow eye involvement due to no incidence [or death] of cell DK17

- the FA40:GD158 and the distinction between elements above the principle diagonal and those below it

- GE40:GE158 which appears to be the cumulative (discounted?) QALY among WSE patients never having had fellow eye involvement

- GF40:GF158 which appears to be the cumulative (discounted?) QALY among all WSE patents

- GG40:GI158 relating to the BSE calculation

- GH40:GH158 averaging between WSE and BSE

Again, as a brief face value check subtracting GF40:GF158 from GE40:GE158 initially results in a positive number with this increasing as time progresses moving down the column but this then starts to fall and turn negative, this possibly giving rise to what appear to be the counterintuitive results around varying the proportion of fellow eye involvement as outlined under clarification point E12 above.

Given the above, please clarify whether you are aware of any other logical errors within:

i. The logical structure as applied within the modelling for the derivation of parameter values as derived from expert opinion

ii. The logical structure as applied within the modelling for the derivation of parameter values as derived from publications within the literature

iii. The logical structure of the electronic model itself

If so, please indicate any changes necessary to correct the model structure and describe the expected impact on the results presented in the submission.