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Single Technology Appraisal (STA)

Dexamethasone intravitreal implant for treating diabetic macular oedema [ID653]

Dear Ms Shergill,

The Evidence Review Group, BMJ Technology Assessment Group (BMJ-TAG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 13 October 2014 by Allergan. In general terms they felt that it is well presented and clear. However, 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 address these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm on Friday 14 November 2014.**

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 Fay McCracken, Technical adviser, (fay.mccracken@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

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Section A: Clarification on effectiveness data

Individual trials

A1. **Priority question:** Please provide the clinical study reports for the NCT00036906 trial and BEVORDEX trials.

A2. Page 22, Table 15 (of the company submission). Please provide the baseline characteristics for the following subgroups in the MEAD-010 and MEAD-011 studies:

a) pseudophakic patients

b) phakic patients

c) treatment naive patients

d) patients who were not treatment naive

A3. Please complete the table below to provide a breakdown of the number of patients at baseline in the full randomised population who were enrolled in MEAD-010 or MEAD-011 because they refused treatment or the investigator decided the patient would not benefit from laser treatment:

	Dexamethasone		**Sham**	
	N	**N**	**n**	**N**
Refused laser at study enrolment				
MEAD-010				
MEAD-011				
Investigator decided patient would not benefit from laser				
MEAD-010				
MEAD-011				

A4. Please conduct a pair-wise meta-analysis of MEAD-010 and MEAD-011 for all outcomes reported in the submission and provide the meta-analysis files and results. Please compare the results of this meta-analysis with the pooled results for MEAD.

A5. Please provide the per protocol results for the best corrected visual acuity outcomes reported in study 024 and an assessment of these in relation to the non-inferiority margins specified.

Mixed treatment comparisons

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A6. **Priority question:** Please provide working WinBUGS code files used for all mixed treatment comparisons (MTCs) (including sensitivity analyses) presented in the submission. Please provide the WinBUGS code files for the competing risks (mutually exclusive) model as well as for the baseline model, including the priors, initial values, and the formatted data.

A7. **Priority question: Page 345** (of the company submission). Please clarify why 12-month data were used in the MTC and not data from any time point given that the relative risks estimated by the MTC were subsequently used to inform the economic model at 3-month cycles assuming constant relative risks.

A8. **Priority question:** As the relative risks used to inform the economic model are assumed not to change over time, there is no need to include only studies reporting 12-month data in the network. Please drop this criterion from included data and re-run the analysis using endpoint data from all the studies meeting the updated eligibility criteria for the MTC analysis (e.g. study NCT00035906 would now be included). Please provide updated WinBUGS files as specified in question A6.

A9. **Priority question: Page 185** (of the company submission). The additional eligibility criteria for the MTC analysis consider only interventions included in the scope as comparators. Please provide the full references of studies that were excluded from the network because of this criterion.

A10. Please provide justification and details of the mixed-treatment comparison model used for evidence synthesis. The competing risks model described in the NICE DSU Technical Support Document 2 is based on the assumption of constant hazards, which appears to be different to the model in the company submission.

A11. Please provide the Deviance Information Criterion (DIC) and a comparison of the residual deviance with the number of unconstrained data points for each outcome when using a fixed and random effects model for the MTC.

A12. Page 201 (of the company submission). Please justify why a binomial likelihood rather than a multinomial distribution (similar to the relative effects model) was used for the baseline model (sham/no treatment) in the MTC. Please also clarify how a dichotomous outcome (loss of at least 10 letters in best corrected visual acuity) was used in the baseline model to provide baseline probabilities for a multinomial distribution.

A13. Page 195 (of the company submission). Please clarify what assumptions have been made in order to split the proportion of patients not achieving a 10-letter improvement into a proportion of patients with 10-letter deterioration and a proportion of patients remaining stable in the BOLT trial in order to consider the data in the mixed-treatment comparison analysis.

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A14. Page 214 and 215 (of the company submission). Please give more details on the mean multiplication factor of 1.989 that was estimated for sensitivity analysis 1 of FAME data, regarding its range and distribution across studies and interventions. Please also provide the assumptions made in order to estimate proportions of patients remaining stable and deteriorating by at least 10-letters for FAME, that were utilised in the mixed-treatment comparison model.

Systematic review

A15. Page 89 (of the company submission). Please provide the rationale for excluding studies with treatment duration of less than 24 weeks from the systematic review.

A16. Page 90, Figure 8 (of the company submission). Please provide the citations for the 34 studies excluded because the treatment duration was less than 24 weeks.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please provide the results for the base-case economic model for the comparisons between DEX700 and watch and wait using data from the pooled MEAD trials (that is, the DEX700 data as is plus the sham arm for watch and wait for the first 3 years of the model).

Please provide the Excel files and tabulated results for the following sub-analyses:

a. Use 3-month transition probabilities for watch and wait from the MEAD sham arm, using the assumption that improvement/worsening by at least 10-letters can only be achieved for the next health state up or down, respectively (this is the current modelling assumption)

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN					
Watch and wait					
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

b. Use the actual 3-month proportions of patients in each of the 6 health states for both DEX700 and W&W from the MEAD trials – in this case, no assumption of moving to adjacent health states is needed and the ACTUAL health states of patients, as observed every 3 months over the first 3 years, can be used.

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN					

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Watch and wait					
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

c. For both DEX700 and watch and wait arms of the economic model, please estimate QALYs for the first 3 years using mean utilities estimated directly from patients' responses on visual function questionnaire utility index, instead of estimating these from the regression model reported in the company submission.

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN					
Watch and wait					
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

B2. **Priority question: Page 386 to 388 and Appendix 18** (of the company submission). The submission reports a number of linear regression models that were tested in order to generate utility values based on visual function questionnaire utility index (with and without adverse events as independent variables) and EQ-5D.

Please provide details of all regression analyses undertaken, in line with the proposed checklist for statistical regression analyses published by Kearns et al. (http://www.nicedsu.org.uk/Regression-methods(2391678).htm), in particular:

a. the type of regression model used to analyse the data, any alternative models tested (e.g. Tobit models) and justification of your final choice;
b. the rationale for the choice of variables included in the model (it is noted that a regression analysis was carried out to determine the impact of raised intraocular pressure and of cataract but no other adverse events, of those included in the economic model, were considered);
c. the handling of missing data;
d. the results of any goodness-of-fit measures used to assess the model.

B3. **Priority question:** Please comment on the following:

a. **Page 391, Table 100 and 101** (of the company submission). Using the reported regression model for visual function questionnaire utility index, the utility values range from 0.62 to 0.79, is this range reasonable and expected for a person with diabetic macular oedema?
b. **Appendix 18** (of the company submission). In the regression analysis that has considered the impact of adverse events, the respective coefficients were not statistically significant at the 5% significance level. However, these coefficients are larger than those related to worse-seeing eye and best-seeing

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eye, implying that adverse events have a higher impact on utility compared with worse-seeing eye and best-seeing eye. Is it reasonable to ignore the impact of adverse events on utility values from the economic model?

B4. **Priority Question:** Please update the economic models using data from the updated MTC analysis as requested in priority question A8. Please provide updated Excel files and tabulated results.

B5. **Priority Question: Page 336-337 Table 71 and 71** (of the company submission).

a. Please clarify how each patient's pair of eyes was each assigned to health states 1 to 6 at baseline. Please report any underlying assumptions or state whether assignment of each eye to a baseline health state was made randomly, based on the baseline distributions of health states as reported on the tables.
b. Please explain why the baseline distribution of best-seeing eye and worse-seeing eye in bilateral DMO was taken from respective DMO eyes in unilateral DMO and was not determined directly from data on the sub-group of patients with bilateral DMO.
c. Please explain why the distribution of eyes in unilateral DMO in the better seeing eye appears to be based on assumptions (rounded figures), and, if so, what these assumptions were.

B6. Page 364, Table 90 (of the company submission). Please confirm that the proportion of 5.80% of vitreous haemorrhage for laser, reported to be from PROTOCOL has been applied to each year separately. Please clarify why for year 3 the model utilised data from year 2 using the last observation carried forward, when year 3 data (9 patients had intraocular pressure greater than 30mmHg in year 3) are available in Allergan 2014 (reference 201). Also, please confirm that figure 5.08% in year 3 is meant to be 5.80%.

B7. Page 331 (of the company submission). Please provide a rationale for using transition probabilities [for MEAD arms] based on observed data for a modified intention to treat (mITT) population, which included only patients who had at least one follow-up visit, instead of data from the ITT population .

B8. Please provide a rationale for not considering fluocinolone acetate in the economic analysis of pseudophakic patients with DMO (either in the base-case analysis or in a scenario analysis).

B9. The economic model has used VFQ-UI for the estimation of QALYs instead of the EQ-5D.

a. Please provide quantitative and qualitative evidence that indicates that EQ-5D performs poorly in patients with DMO, as per NICE recommendations for

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submissions utilising an alternative utility measure (Guide to the methods for technology appraisal 2013, section 5.3.10).

b. Please provide more details on the methods used to generate the new utility index, their validity and an estimation of how use of the new measure may have affected the resulting utility values, as per NICE recommendations (Guide to the methods for technology appraisal 2013, section 5.3.10).

B10. Page 330, Table 68 (of the company submission). Please provide a rationale for using LOCF from year 2 for patients receiving laser treatment in the model "DMO_NICE_Oct2014_Pseudophakic_All_Tx" when week 104 (17.6%), 128 (10.8%) and 156 (9.7%) data are available in Allergan 2014 (reference 201).

B11. Page 37, Table 3 (of the company submission). The 'average cost of a course of treatment' row states that an average of 4.47 treatments over 3 years are expected. However, the 'anticipated average interval between courses of treatments' row in the same table states that patients will receive treatment at intervals of approximately 6 months. These statements seem to contradict each other. Please clarify the average number of treatments that a patient receiving DEX700 will have.

B12. Page 28, Table 2 (of the company submission). Please clarify the difference in total costs between dexamethasone and ranibizumab when ranibizumab is at a 50% discount.

Section C: Textual clarifications and additional points

C1. Page 409, Table 111 (of the company submission). Please explain why no intraocular pressure (IOP) checks have been applied to fluocinolone, as this is a corticosteroid and has the potential to raise IOP.

C2. Page 669, Table 260 (of the company submission). The ERG is able to verify the discontinuation due to adverse events (and other reasons) in month 23 *'Inp_Treatment'!AJ98* for bevacizumab in the model "DMO_NICE_Oct2014_Pseudophakic_All_Tx" based on Rajendram et al., 2012 (reference 200) which states 6 out of 42 patients discontinued the intervention in the bevacizumab arm during year 2. However, the ERG is unable to verify the 7.14% discontinuation rate used in years 3 to 5 in the references (Rajendram et al., 2012; Michaelides et al., 2010). Please clarify how a rate of 7.14% was estimated and the reference (with page number and/or table) used.

C3. The ERG is unable to verify discontinuation due to adverse events (and other reasons) or lack or loss of efficacy for ranibizumab in the models "DMO_NICE_Oct2014_Pseudophakic" and "DMO_NICE_Oct2014_Pseudophakic_All_Tx" based on the RESTORE references in

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Table 260 (Lang et al., 2004; Mitchel 2011; Schmidt et al., 2014).

a. Please clarify which reference (with page number and/or table) was used to estimate a discontinuation rate due to adverse events of:
   - 9.48% in month 11 'Inp_Treatment'!S97
   - 6.02% in month 23 'Inp_Treatment'!AJ97
   - 3.85% in month 35 'Inp_Treatment'!BA97
   - 6.45% in month 47 'Inp_Treatment'!BR97
   - 6.45% in month 59 'Inp_Treatment'!CI97
b. Please clarify which reference (with page number and/or table) was used to estimate a discontinuation rate, due to a lack or loss of efficacy of:
   - 0.86% in month 11 'Inp_Treatment'!S114
   - 0.29% in month 47 'Inp_Treatment'!BR114
   - 0.29% in month 59 'Inp_Treatment'!CI114

C4. The ERG is unable to verify the proportion of patients receiving fluocinolone and the proportion of patients discontinuing due to adverse events (and other reasons) in model "DMO_NICE_Oct2014_All DMO_incl.FAME " using the FAME references Campochiaro et al., 2011; Campochiaro et al., 2012; Cunha-Vas et al., 2013.

a. Please clarify which reference (with page number and/or table) has been used to estimate a proportion of 26% of patients receiving fluocinolone in the model for:
   - month 12 'Inp_Treatment'!Y61
   - month 24, 'Inp_Treatment'!AP61
   - month 26, 'Inp_Treatment'!BG61
   - month 48, 'Inp_Treatment'!BX61.
b. Please clarify which reference (with page number and/or table) was used to estimate a discontinuation rate of:
   - 20% due to adverse events for month 23, 'Inp_Treatment'!AJ97
   - 9% month 35, 'Inp_Treatment'!BA97
   - 14.5% month 47, 'Inp_Treatment'!BR97
   - 14.5% month 59, 'Inp_Treatment'!CI97

C5. Please provide details on the methods of identification and selection for the following papers as data sources for the economic model, and the rationale for the data used:

a. Mulnier et al., 2006: mortality for patients with diabetes
b. Hirai et al., 2008: mortality attributable to DMO in patients with diabetes
c. Christ et al., 2008: mortality in people with severe loss of vision
d. Mitchell et al., 2012: natural progression of vision loss due to DMO
e. Colquitt et al., 2008: cost of severe vision loss

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C6. Page 397, Figure 65 (of the company submission). Please provide the references for the 3 'resource use' studies identified in the systematic literature review, the full text of which the company were unable to access.

C7. Page 520, reference 194 (of the company submission). The ERG is unable to differentiate between Table 03.1.4-1001 and Table 03.1.4-1019 in 'Allergan Inc. Clinical Story 024 Final. 2014'. Both tables are titled "Fellow Eye Occurrence in diabetic macular oedema and Receipt of Treatment During the Study". Please clarify the difference between these 2 tables and if Table 03.1.4-1019 has been used to estimate the % of DEX700 arm patients in MEAD who were affected unilaterally at baseline and developed fellow eye involvement over the study duration using the broad definition of diabetic macular oedema for the base case.

C8. Section 12.5.4.2, Table 12 to 21 and Table 14.6 to 3.5 (of the company clinical study reports).

a. Please clarify whether the data reported in the clinical study reports (number (%) of patients with cataract surgery in the study eye subgroup: phakic patients at baseline)) are cumulative?
b. In addition there is a discrepancy between the models and the submission, please clarify which value is the correct value to be used in the model and the reason for this difference.

Parameter	Model reference	Submission reference
Cataract extraction rate DEX700 PRN: Year 1	'Inp_AE'!F15 8.40% =(9+13) / (117+145)	Page 360 Table 85 6.49%
Cataract extraction rate DEX700 PRN: Year 2	'Inp_AE'!G15 19.17% =(19+27) / ((117+145) - (9+13))	Page 360 Table 85 21.22%
Cataract extraction rate DEX700 PRN: Year 3 to 5	'Inp_AE'!H15 2.94% =(3+3) / ((117+145) - (9+3+19+27))	Page 360 Table 85 18.13%

C9. The cataract extraction rate for fluocinolone acetonide in year 2 is 65.53% based on "FAME: 154/235 phakic patients required cataract surgery to end of Year 2" in DMO_NICE_Oct2014_All DMO_incl.FAME 'Inp_AE'!I19. However, the ERG believes it is incorrect to estimate this rate based on the population from Campochiaro et al.,

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2012 with a duration of 36 months (188 out of 235 (80%) patients) and events from Campochairo et al., 2011 with a duration of 24 months (154 out of 375 (41%) patients). Please explain why these figures were used for the estimation of the final 65.53%.

C10. Page 340, Tables 74 and 75 and all Tables in Appendix 15 (of the company submission). Please confirm that these tables present 3-month transition probabilities for DEX700 AFTER the assumption that transitions may be made only to the adjacent health state up or down and thus are not representative of transition probabilities, as recorded in the MEAD DEX700 arm.

C11. Page 379 and 380 Figure 63 (of the company submission).

a. Please provide a rationale for the strict inclusion criteria (data relating to best-corrected visual acuity or adverse events, only patients with diabetic macular oedema) used for the identification of health-related quality of life studies.
b. Please also provide full references of the 6 studies the full text of which the company were unable to access, as stated in the flow diagram in Figure 63.

C12. Page 195 (of the company submission). Please explain what is meant by the 'analysis windows' reported in the submission.

C13. Page 161 (Figure 18), page 166 (Figure 21) and page 169 (Figure 22) (of the company submission). Please explain the difference in the numbers of patients in each arm in the 'cataract surgery to last best-corrected visual acuity' analysis compared with the 'cataract adverse event to cataract surgery' analysis.

C14. Page 349 (of the company submission). Beyond the study duration the discontinuation rates have been extrapolated using the average rate over the study duration applied in line with the relevant study cycle length". Please confirm that this applies only to studies with duration lower than 3 years, as the base-case analysis assumes treatment is terminated after 3 years so no discontinuation should be applied after that period.

C15. Page 100, Table 12 (of the company submission). Please provide an explanation for inclusion of the Udaondo et al 2013.

C16. Page 229 to 238 (of the company submission). The flow chart of non-randomised control trials reports 10 studies meeting eligibility criteria but only nine appear to have been described. Please clarify the correct number and provide details of any missing studies.

C17. Page 268 (of the company submission). Please provide the definitions used for 'the expected levels of IOP elevation' and 'cataract' in the adverse events.

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C18. Page 285, Table 58 (of the company submission). Please provide the criteria that would be used in clinical practice to select patients for whom DEX700 treatment would be suitable in terms of the patients "insufficiently responsive to laser" as provided for the other patient populations detailed in the table.

C19. Please provide an explanation as to why the following baseline data have been extracted exclusively from the MEAD DEX700 arm and not from the mixed MEAD DEX700 and sham study sample:

a. Page 314 (of the company submission). The proportions of patients within the cohort who have unilateral diabetic macular oedema in the BSE or the WSE, or bilateral diabetic macular oedema at baseline.
b. Page 352 (of the company submission). The proportion of patients within the cohort who develop fellow eye involvement.

C20. Please confirm that the economic analysis used DEX700 as baseline treatment, and that the following references to sham as baseline treatment, should be amended:

a. Page 331, Table 69 (of the company submission): ("3-monthly probabilities [...] generated from the sham arm...")
b. Page 343 (of the company submission): "...the transition probabilities generated by applying the relative risks to the transition probabilities for watch and wait were normalised.."
c. Page 364 (of the company submission): "transition probabilities [...] were based on watch and wait (sham) patients' transitions in the MEAD studies [...]. DEX700 and active comparator transition probabilities were calculated from these by applying relative risks [...] calculated from the network meta-analysis."

C21. Page 361, Table 86 (of the company submission). There is a discrepancy between the model "DMO_NICE_Oct2014_Pseudophakic_All_Tx" 'Inp_AE'!C39 and Table for the proportion of raised intraocular pressure in year 1 for laser treatment. The model uses a value of 1.02% whereas the submission presents a value of 0.01%. Based on Table 03.2.1-1077 in Allergan 2014 (reference 201), please confirm that 1.02% (3/293) is the correct value.

C22. Page 336, Table 71 (of the company submission). Please provide the missing footnotes for better-seeing eye and worst-seeing eye (1-4).

C23. Page 678, Appendix 19. Please clarify whether and if so how the discounting formula described was used, as it is not referred to in the text.

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C24. Page 2 to 11. Please check and amend the page numbers in the list of tables as some of these appear to be incorrect.

C25. Page 89 and 90, Figure 8. There are some discrepancies in the text on page 89 compared with the details provided in the PRISMA diagram, Figure 8 on page 90. Please clarify which numbers are correct.