NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dexamethasone intravitreal implant for treating diabetic macular oedema

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. Comments are pasted in verbatim and represent the views of consultees and commentators. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment (sic)	Response
Allergan	**Has all of the relevant evidence been taken into account?** Allergan considers that all evidence deemed relevant at the time of submission was presented and has been taken into account by the Evidence Review Group (ERG) and the Committee. Further to specific points raised at the appraisal committee meeting and that were subsequently highlighted in the ACD, we recognise that additional relevant evidence could be helpful to allow the Committee to more robustly assess dexamethasone in the population of patients with a natural lens who either do not respond to, or are not suitable for, non-corticosteroid therapies. We would therefore like to draw your attention to a new, highly relevant, analysis presented in the Appendix of this document, which we believe is likely to affect the preliminary recommendations in the ACD because it will reduce the uncertainty around the ICER in this specific subgroup and give the Committee enhanced confidence that the ICER for this population may be within the range normally considered to be a cost-effective use of NHS resources (up to £20,000–£30,000 per QALY gained). This new analysis results in an ICER of £14,978 and incorporates the following in addition to changes recommended by the ERG and the Committee: • A new analysis of the MEAD trial data which aims to better approximate visual outcomes for the high proportion of patients who were censored or who discontinued from the studies in both the sham and the DEX700 treatment arms, which the Committee noted had likely contributed to the overestimation of the reported ICER when the observed MEAD data alone was considered in pairwise analysis (section 4.19 of the ACD). • The incorporation of alternative and highly relevant utility values from the literature. These are based on Czoski-Murray *et al.*[1] which provides a wider range of utility values than those observed in the MEAD studies, noted by the Committee as an additional possible contribution to the overestimation of the reported ICER (section 4.19 of the ACD). This is consistent with the	Comments noted. Details of the Committee's consideration of the company's new evidence are given in sections 4.21–4.25 of the FAD.

Consultee	Comment (sic)	Response
	approach taken in the assessment of other technologies for this condition, recognising the complexities surrounding direct utility elicitation in this population. For completeness utility values from Brown[2] and Brown *et al*.[3] have also been included in additional analyses. • The incorporation of a clinical continuation rule for DEX700, whereby patients are assumed not to receive further treatment with DEX700 if they do not achieve a gain of at least 5 letters between baseline and Month 6, following their first injection of DEX700.	
Allergan	**Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** Allergan believes that, in general, the summaries of clinical and cost effectiveness included within the ACD are a reasonable interpretation of the evidence; however, we would like the Committee to consider some points of clarification regarding the interpretations of the evidence. In section 3.24 of the ACD it is stated that: "*The company also noted that the 95% credible intervals were wide, denoting uncertainty around the true amount of heterogeneity*". We would like to challenge this interpretation of the submitted evidence. The statement should read: "*The company also noted that the 95% credible intervals around the estimated amount of heterogeneity were wide, denoting uncertainty around the true amount of heterogeneity*".	Comment noted. Section 3.24 of the FAD has been amended to state that the 95% credible intervals around the estimated amount of heterogeneity were wide.
Allergan	Section 3.27 of the ACD discusses the comparison of results from the pairwise meta-analysis of MEAD-010 and MEAD-011 with the results from the network meta-analysis. The discussion states that this comparison: "*showed that the relative risk from the pairwise meta-analysis of losing 10 or more letters was 0.72 (95% CrI 0.35 to 1.25) which is different to the relative risk from the network meta-analysis of 0.71 (95% CrI 0.41 to 1.08). The relative risk for gaining at least 10 letters at 12 months from the pairwise meta-analysis is 1.35 (95% CrI 0.77 to 2.21) which differs from the relative risk from the network meta-analysis of 1.40 (95% CrI 0.92 to 2.14)*".	Comment noted. Section 3.27 of the FAD has been amended.

Consultee	Comment (sic)	Response
	Allergan would like to query the conclusion that the estimates of the relative risk of losing 10 or more letters and the relative risk of gaining at least 10 letters were different between the pairwise meta-analysis and the network meta-analysis. We believe that the presented results (0.72 vs 0.71 for the relative risk of losing 10 or more letters and 1.35 vs 1.40 for the relative risk of gaining at least 10 letters from the pairwise vs network meta-analysis) are comparable. Further, in both analyses the 95% credible intervals shows no statistically significant difference, and hence the conclusions of the two analyses are the same. However, there is some additional uncertainty in the pairwise meta-analysis, which is expected due to only the MEAD trials being included in the pairwise analysis (whereas additional trials are included in the network meta-analysis alongside the MEAD trials) and the uncertainty is driven by the number of trials included in the analysis, their size and their quality.	
Allergan	In section 3.58 of the ACD it is stated that: "*The ERG agreed that the use of the MEAD sham data is likely to have overestimated the true efficacy of watch–and–wait; however, they highlighted that the MEAD trials were the only ones in the network meta-analysis that provide relative effects for dexamethasone intravitreal implant compared with sham, and so these relative effects are also present in the results from the network meta-analysis*". Allergan believes that there has been some confusion regarding the interpretation of relative risks from the network meta-analysis. The statement above would be correct if the results of the network meta-analysis were presented in terms of relative treatment effects. However, the outputs presented in the submission were relative risks, constructed using the absolute probabilities of being in each category of vision and influenced by all four trials, including a sham treatment arm (i.e. the MEAD studies[4], ETDRS[5] and Olk[6]). The probability for sham was calculated by fitting a baseline model to the sham arms of the lowest category of the ordered categorical model (i.e. losing at least 10 letters) from all trials that include a sham treatment arm (i.e. the MEAD studies,[4] ETDRS[5] and Olk[6]). The treatment effect model estimated relative treatment effects and applied these to this probability for sham (calculated from the baseline model) to yield probabilities of all other treatments being in each category of vision. These probabilities were used to calculate the relative risks (e.g. probability of treatment/probability of sham) which were reported in the network meta-analysis section of the submission and used in the economic modelling.	Comment noted. The ERG acknowledged the company's comment but considered the statement in section 3.58 of the ACD to be factually correct. No change made to the FAD.
Allergan	In section 3.64 of the ACD it is stated that: "*The ERG noted that the company did not present data for fluocinolone acetonide*	Comment noted. The ERG acknowledged the company's comment but considered the statement in section 3.64 of the ACD to be factually correct.

Consultee	Comment (sic)	Response
	intravitreal implant in combination with laser photocoagulation or data for bevacizumab in combination with laser photocoagulation". Allergan would like to clarify that it attempted to identify evidence for fluocinolone acetonide intravitreal implant in combination with laser and for bevacizumab in combination with laser as part of the systematic review of the clinical evidence base of randomised controlled trials described in Section 6.1 and 6.2 of the manufacturer's submission; however, no relevant evidence was identified for these two treatment strategies.	No change made to the FAD.
Allergan	In section 3.68 of the ACD it is stated that: "*the poor fit of the models to the datasets (as indicated by the between study standard deviation)*" This was later described as a reason why the ERG were concerned about the validity of the results of the network meta-analyses. Allergan does not agree with this interpretation for the following reasons: Model fit is not assessed by between-study standard deviation, but instead by using goodness-of-fit measures, such as the deviance information criterion – which allows a comparison of goodness-of-fit between different models – or the total residual deviance – which assesses the overall fit of a particular model. Between-study standard deviation measures how much statistical heterogeneity there is amongst the evidence. This value is independent of model fit. When model fit was assessed using total residual deviance, even though this value was higher than the number of individual data points included in the model, the model was considered a sufficient fit to the data using the Chi-squared statistical test, as noted in the manufacturer's submission Section 6.6.7.	Comment noted. Section 3.75 of the FAD has been amended to read "the poor fit of the models to the datasets (as indicated by the residual deviance)".
Allergan	In sections 4.2, 4.16 and 4.17 of the ACD it is noted that the Committee considered there to be populations of DMO patients with a pseudophakic lens who would be eligible for treatment with DEX700 which are further defined by a central retinal thickness (CRT) cut-off of at least 400 micrometres or less than 400 micrometres. Whilst Allergan understands that this distinction (which has important implications for comparators) has been made in light of the guidance from technology appraisal 274[7], Allergan does not feel that this was made clear in the ACD. Allergan is concerned that the reader could incorrectly believe that conditions based on CRT form part of the licence for DEX700 and would therefore appreciate the Committee appropriately reconsidering their wording around these sub-populations.	Comment noted. Section 4.2 of the FAD has been amended to include a cross-reference to the marketing authorisation for dexamethasone intravitreal implant. It has also been clarified that the populations have been defined according to comparators as well as the marketing authorisation for dexamethasone intravitreal implant.
Allergan	In section 4.8 of the ACD, the Committee noted that: "*the company had provided subgroup analyses for people with a pseudophakic lens,*	Comment noted. No change to the FAD requested or required.

Consultee	Comment (sic)	Response
	but not for people whose condition did not respond to non-corticosteroid treatment, or for whom it was not suitable". As discussed in section 7.2.1 of the submission dossier, Allergan would like to highlight that there is no specific evidence available for DEX700 or sham in the population of patients for whom non-corticosteroid treatment was not suitable. Therefore, in the absence of these data, the assumption was made that there is no differential efficacy of DEX700 or sham in this population compared with the total population of the MEAD studies. Further, there is limited evidence available for DEX700 or sham in the population of patients whose condition did not respond to non-corticosteroid treatment; however, available evidence does not suggest that there is a differential efficacy in this population compared with the total population. Therefore, in the absence of robust data, the assumption was made that there is no differential efficacy of DEX700 or sham in this population compared with the total population of the MEAD studies. Allergan considers these to be reasonable assumptions given that these populations are covered by the licence for DEX700 in DMO which was granted by the European Medicines Agency based on the results of the MEAD studies for the total population. Patients enrolled in MEAD had previously received laser therapy or were not considered suitable candidates for such therapy. Whilst only a small proportion of patients from the MEAD trials programme had previously received anti-VEGF treatment, given the broader anti-inflammatory action of steroids compared with anti-VEGF agents, the CHMP felt it was reasonable to assume that steroids would be tried in patients with DMO who had not responded to anti-VEGF therapy, or who were unsuitable for anti-VEGF injections, irrespective of lens status in current clinical practice.	
Allergan	In section 4.9 of the ACD it is stated that: "*if the vision of patients in the sham procedure arm did not improve during the trial, they were offered treatment with dexamethasone intravitreal implant and then excluded from the trial*". Allergan believes that this statement misrepresents the reality of what happened to sham patients in the MEAD studies, particularly as sham patients were not necessarily treated with DEX700 if they were deemed to require additional treatment by their physician. The statement should read: "*if the vision of patients in the sham procedure arm was considered to require additional treatment during the trial, the patients were offered appropriate treatment and then excluded from the trial*".	Comment noted. Section 4.9 of the FAD has been amended to improve its accuracy.

Consultee	Comment (sic)	Response
Allergan	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Allergan would like the opportunity to discuss further the conclusion made in section 4.19 of the ACD that states: "*The Committee noted that, although it preferred using the head-to-head MEAD trial data, the ICER of £1,166,271 per QALY [quality-adjusted life year] gained was likely to be an overestimate because of the high discontinuation rates in MEAD (leading to the sham arm being unrepresentative of patients in clinical practice) (see section 4.9), narrow bands of utility values from MEAD (see section 4.14) and the possibility of the WSE [worse-seeing eye] having a higher utility value than the BSE [better-seeing eye] in the model (see section 4.15). The Committee acknowledged that although the true value of the ICER was likely to be less than £1,166,271 per QALY, it was extremely unlikely to be within the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained). The Committee concluded that dexamethasone intravitreal implant was not a cost-effective use of NHS resources compared with watch–and–wait for treating people who do not have a pseudophakic lens and have DMO that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them, and that it did not recommend dexamethasone intravitreal implant for this group.*" Allergan welcomes the Committee's reasoning that the ICER given in this paragraph is likely to be an over-estimate, but we respectfully disagree with its conclusion that the true ICER is unlikely to show cost-effectiveness according to NICE's normal range. Based on the analysis which we present in the Appendix to this letter; which uses head-to-head MEAD trial data, includes a clinical continuation rule and explores ways of handling discontinuation which better characterises the trajectory of change in visual function for affected patients; the ICER we show for patients who both still have their natural lens and who are unresponsive to or unsuitable for non-corticosteroid treatment falls to £14,978, which does indeed demonstrate cost-effectiveness. We commend this analysis to the Committee on the basis that it should give the Committee increased confidence that the ICER for this population may be within the range normally considered to be a cost effective use of the National Health Service (NHS) resources and therefore lead to a positive recommendation for an important group of patients who have high unmet clinical need and who are currently excluded from the draft recommendation.	Comment noted. See sections 4.21–4.25 of the FAD for details of the Committee's consideration of the company's new analysis submitted in response to the ACD.

Consultee	Comment (sic)	Response
Allergan	**Other points of clarification** In sections 3.20, 3.23 and 3.44 of the ACD the DRCR.net PROTOCOL I study is incorrectly referred to as PROTOCOL 1.	Comment noted. The spelling of the PROTOCOL I study has been corrected in sections 3.20, 3.23 and 3.44 of the FAD.

Comments received from clinical experts and patient experts

None

Comments received from commentators

Commentator	Comment	Response
Alimera Sciences	**Clinical interpretations** 1. The first issue relates to the 'watch-and-wait' therapy (i.e., no active treatment received). We would like to highlight that 'watch and wait' is not a standard of care (SOC) for patients with DMO. It is also potentially detrimental to the patient's outcome, with nearly half of the patients developing DMO losing two or more lines of visual acuity within 2 years.[4] Furthermore, watch-and-wait therapy is not a position supported by clinical practice as physicians using FAc implants in patients with DMO do so according to the recommendations of the NICE technology appraisal TA301[4] and this is when the patient shows an insufficient response to first-line therapy. Since November 2013, the usage of ILUVIEN in clinical practice has been growing with 141 hospitals registered to receive ILUVIEN and 65% of all UK hospitals having treated at least one patient with ILUVIEN. This usage is reflected in the increasing number of published case reports.[6-11]	Comment noted. As described in section 4.5 of the FAD, the Committee heard from the clinical experts that people with DMO that is insufficiently responsive to non-corticosteroid therapy who do not have a pseudophakic lens are monitored but do not have active treatment (also known as 'watch–and–wait'). No change to the FAD required.

Commentator	Comment	Response
Alimera Sciences	2. The second objection relates to the appropriate comparator for DMO patients with a pseudophakic lens. In current practice, NICE recommends the use of the FAc implant in patients as "…an option for the treatment of chronic diabetic macular oedema considered insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens." [4] Hence the SOC and the logical comparator to DEX is the FAc implant, given that this is approved for use in DMO patients with a pseudophakic lens and in patients that do not respond to non-corticosteroid treatment. Current practice is also reflected by the views of the ERG. Indeed, they expressed concern that FAc implant was not included in the base case analysis for patients who had a pseudophakic lens and for patients with disease that has not had an adequate response to non-corticosteroid therapy. (pp. 31, point 3.74).[2]	Comment noted. The evidence considered by the Committee for people with a pseudophakic lens and with diabetic macular oedema that does not respond to non-corticosteroid treatment or such treatment is unsuitable for them included a comparison with fluocinolone intravitreal implant (see section 4.26 of the FAD). No change to the FAD requested or required.
Alimera Sciences	3. The third point relates to the uncertainty of the clinical efficacy of DEX. The clinical studies included patients that were naïve to DMO therapy in addition to patients that were insufficiently responsive to non-corticosteroid therapy.[12] The CHMP states that "While one of the two pivotal studies (study 206207-010) achieved statistically significant improvement in the primary endpoint, the other study (206207-011) failed to show superiority of DEX. In this study, the difference in mean BCVA average change from baseline compared to Sham was not significant for either dose of dexamethasone. Furthermore, the clinical relevance of an average increase of 1 to 2 letters over the 3 year study period (1.4 in the pooled analysis compared to Sham) was considered questionable by the CHMP." (pp. 68).[12] Pivotal trials were therefore inconclusive, showing an average benefit of a mere 1.4 letters in BCVA over 3 years.	Comment noted. No change to the FAD requested or required.
Alimera Sciences	4. The fourth point relates to the appraisal committee's preliminary recommendations for DEX. The CHMP showed that in patients that had already received treatments for DMO (i.e., laser, steroid or anti-VEGF treatment; non-corticosteroid treatments) prior to the start of the study there was an overall gain in letters that was similar to the overall population (a mean gain of +1.4 letters; see point 3 above). This then led the CHMP to question the clinical relevance of this data by stating "…this population may have had more stubborn disease than treatment naïve patients, hence contributing to the limited treatment benefits observed." (pp. 68).[12] Available data therefore questions the relevance of the appraisal committee's preliminary recommendations for the use of DEX.	Comment noted. No change to the FAD requested or required.

Commentator	Comment	Response
Alimera Sciences	**Cost-effectiveness interpretations** 1. The models comparing the cost-effectiveness of therapies for patients with DMO that have not responded adequately to non-corticosteroid therapy clearly show that for all comparisons, except at a discount of 10%, FAc implant dominated dexamethasone intravitreal implant. This was based on a list price of £5,500 for FAc implant which the manufacturer makes available to the NHS under the terms agreed with the Department of Health as part of a patient access scheme (pp. 23, point 3.52).[2]	Comment noted. Minor amendments have been made to the wording of section 3.52 of the FAD to make this clearer.
Alimera Sciences	2. Using the models comparing the cost-effectiveness of therapies for patients with DMO that have a pseudophakic lens and disease that does not respond adequately to non-corticosteroid therapy, or such treatment is not suitable for them, the ERG stated that with a 40% and 50% discount in the price of FAc implant, it dominated DEX (pp. 38, point 3.91).[2]	Comment noted. No change to the FAD requested or required.
BMJ Evidence Review Group	Para 4.12, second bullet point: "for people with a pseudophakic lens, the company presented a comparison of dexamethasone intravitreal implant with ranibizumab in its base-case and with bevacizumab and watch–and–wait as a scenario analysis": Minor factual error: you need to add "laser" in the scenario analysis.	Comment noted. Section 4.12 of the FAD has been amended accordingly.
BMJ Evidence Review Group	Para 4.20 (and actually my comment refers to the whole recommendation): "The Committee considered the cost effectiveness of dexamethasone intravitreal implant compared with fluocinolone acetonide intravitreal implant for people who have a pseudophakic lens and DMO that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them [...] it considered that the cost effectiveness of dexamethasone intravitreal implant is likely to be similar to fluocinolone acetonide intravitreal implant". Has the Committee taken into account that the company's comparison is for the TOTAL POPULATION and not the pseudophakic one? Have the results for the TOTAL POPULATION been used as a proxy for the pseudophakic population? I note that fluocinolone has higher rates of cataract requiring extraction in phakic patients (see ERG report, page 214). This means that the fluocinolone outcomes in the total population have been more negatively affected by cataract formation compared with dexamethasone, so may in fact be more effective than dexamethasone (and not similar to it) in the pseudophakic population. I think this point may need to be discussed further and clarified in the FAD.	Comment noted. The Committee made its recommendation after considering the best available clinical- and cost-effectiveness evidence for this comparison. No change to the FAD required.

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<tr><th>Commentator</th><th>Comment</th><th>Response</th></tr>
<tr><td>Novartis</td><td>

1. Has all of the relevant evidence been taken into account?

<u>Systematic Review & Network Meta-analysis</u>

Novartis conducted a systematic review and network meta-analysis in DMO relevant to the NICE decision problem in Q1 2014. The outputs of this work were published on July 16th in PLOSone journal[1].

The manufacturer appears not to have considered all the appropriate and relevant evidence within their network meta-analysis. Of significance and impacting the effect size of ranibizumab was the omission of other key evidence (central to the decision problem). Table 1 below highlights the evidence that was omitted from the manufacturer's network meta-analysis.

Table 1. Key evidence omitted from the manufacturer's network meta-analysis and relevant to the decision problem

<table>
<tr><th>Treatment Node</th><th>Omitted Evidence</th></tr>
<tr><td>Ranibizumab</td><td>READ-2 [2]

RESOLVE[3]</td></tr>
</table>

In addition to the omissions as described above, the manufacturer has chosen to *include* the REVEAL study[4] as part of the network to inform the relative effectiveness estimate of ranibizumab. This study evaluated ranibizumab in an *exclusively* Asian population and is thus not representative of the UK wider population. Consequently, it should not be included within this evidence network for reasons of heterogeneity of inclusion criteria compared to the other studies.

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Comment noted. RESOLVE and READ-2 were appropriately excluded from the company's NMA because the ranibizumab treatment regimens used do not reflect the SPC.

REVEAL was appropriately included in the company's NMA because it uses the ranibizumab treatment regimen recommended in the SPC and, other than the difference in ethnicity, the baseline characteristics are comparable with the other trials in the NMA. No changes to the FAD have been made.

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Commentator	Comment	Response
Novartis	**2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Page 10, Section 3.20.** The ACD document incorrectly describes the PROTOCOL **1** study – the study is called the PROTOCOL **I** study (i.e. the letter "I" not the number "1").	Comment noted. The spelling of PROTOCOL I has been corrected in section 3.20 of the FAD.
Novartis	**Pages 15-16, Section 3.32.** In terms of the model structure, Novartis notes that the manufacturer uses two very wide Markov states at the high and low ends of visual acuity (compared to 10 letter states in the rest of the structure). Specifically the use of "76 letters or more" AND "35 letters or less" rather than splitting the states into: High visual acuity: 2 states – one for "76-85 letters" and another for "86-100 letters." Low visual acuity: 2 states – one for "26-35 letters" and another for "≤25 letters." The net effect of the manufacturer's model structure is reduced granularity and QALY underestimation – i.e. the ability to be able to calculate incremental differences in utility between treatments. The various models of utility that have been applied to technology appraisals in this field have linear functions (please see Table 2 [provided but not reproduced]) and thus utility differences that occurred are *lost* when using this homogenised upper and lower state structure. This approach favours less effective treatments as is the case within the present context and might have led to overly optimistic ICERs for dexamethasone. Furthermore, the manufacturer's invalid assumption that a patient may only transition by a maximum of 1 state in a cycle further exacerbates the problem of QALY underestimation.	Comment noted. No change to the FAD requested or required.

Commentator	Comment	Response
Novartis	**Pages 18-19, Section 3.39.** Novartis also notes that the manufacturer does not undertake sensitivity analyses with the utility algorithms that have already been applied within the context of recent NICE decision making (in TA274[10]) and the ongoing appraisal for aflibercept in DMO. Instead the manufacturer undertakes a sensitivity analysis with EQ-5D, which is known to be insensitive to vision related diseases[7, 8]. Novartis feels that it is appropriate to ensure that the methodology associated with NICE decision making is harmonised between appraisals where possible. The utility algorithms selected by the manufacturer for the present submission favour less effective treatments since the delta between the highest and lowest vision states is significantly smaller: 0.16 was the maximum delta presented at the committee meeting for the manufacturer's choice of utility data compared to 0.50 for Czoski-Murray[5] and 0.41 for Brown (1999)[6]. As a consequence, the economic modelling is underestimating the ICERs for the dexamethasone comparisons. It is also worth noting the perverse irony in the choice of utility algorithm employed by the manufacturer for their base case - Visual Function Questionnaire Utility Index (VFQ UI), calculated directly from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) collected in the MEAD clinical trials. The results demonstrate that dexamethasone **is no more effective than sham** at improving health related quality of life (defined by NEI VFQ-25) on both the composite score and individual items as reported on page 7 of the ACD and discussed at the committee meeting: "3.11. There were no statistically significant differences in the mean average change in health-related quality of life when comparing dexamethasone intravitreal implant with sham procedure in the MEAD trials (overall composite score: dexamethasone 1.9 versus sham 2.2, p=0.64; general vision: dexamethasone 4.5 versus sham 5.0, p=0.92; difficulty with near vision: dexamethasone 5.8 versus sham 4.3, p=0.25; difficulty with distance vision: dexamethasone 2.9 versus sham 2.7, p=0.70; mental health symptoms due to vision: dexamethasone 4.6 versus sham 4.8, p=0.89)."	Comment noted. The company provided new evidence in response to the ACD that included cost-effectiveness estimates generated using utility values derived from published data that had been discussed in previous appraisals. The Committee's consideration of the utility values employed by the company is given in sections 4.14 and 4.23 of the FAD.

Commentator	Comment	Response
Novartis	**Page 20, Section 3.41.** "For ranibizumab, the total cost was £858.85 for unilateral disease and £1659.36 for bilateral disease" Novartis requests that the additional words "without PAS" are added to the sentence for clarity.	Comment noted. Section 3.41 of the FAD has been amended so it is clear the costs are based on ranibizumab's list price.
Novartis	**Page 20, Section 3.43.** The assumptions employed by the manufacturer for the number of monitoring visits with ranibizumab (based on the summary of product characteristics and TA237) are out of date since the ranibizumab SmPC has changed and does not require monthly monitoring: Please see precise wording from Section 4.2 of the ranibizumab SmPC[9]: "…monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography)."	Comment noted. As written in the consultation response, monitoring and treatment intervals should be determined by the physician, which does not necessarily mean the assumption made in the company submission is inappropriate. No change to the FAD requested or required.
Novartis	**Page 21, Section 3.44.** The ACD document incorrectly describes the PROTOCOL 1 study – the study is called the PROTOCOL I study (i.e. the letter "I" not the number "1").	Comment noted. The spelling of PROTOCOL I has been corrected in section 3.44 of the FAD.

Commentator	Comment	Response
Novartis	**Page 22, Section 3.46.** "In people with a pseudophakic lens, treatment with ranibizumab resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £50,905 per QALY gained…" Please could the additional words, and "not stratified by retinal thickness of >400 micrometres" be added to make it clear that this ICER is for the full pseduophakic DMO population.	Comment noted. Section 3.46 of the FAD has been amended to specify that this is the full population of people with a pseudophakic lens.
Novartis	**Page 31, Section 3.73.** "The restriction of transitions between health states for each cycle, so that each patient could only move 1 BCVA health state per cycle" Novartis agree with the ERG that this assumption is not valid. It is important to recognise the collective effects of several of the manufacturer's key modelling assumptions (model structure, utility source, and the state transition restrictions as here) all leading to reduced granularity and favouring dexamethasone.	Comment noted. No change to the FAD requested or required.
Novartis	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Novartis agrees that the provisional recommendations are sound and a suitable basis for guidance to the NHS.	Comment noted.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	3.29	In section 3.29, the ACD refers to â€˜Watch and waitâ€™, or no treatment, as current practice where patients are no longer responding to first line therapy, currently ranibizumab. We feel that this is no longer clinical practice, and likely to be detrimental to good outcomes for patients. Specifically in patients with a pseudophakic lens, the comparator used in the analysis was ranibizumab. Clearly if such a patient is no longer sufficiently responding to 1st line treatment, TA301 states that ILUVIEN should be considered as an option. The choice of comparator therefore should be ILUVIEN	Comment noted. As described in section 4.5 of the FAD, the Committee heard from the clinical experts that people with DMO that is insufficiently responsive to non-corticosteroid therapy who do not have a pseudophakic lens are monitored but do not have active treatment (also known as 'watch–and–wait'). No change to the FAD required.
Pharmaceutical Industry 1	1.1, 4.6, 4.17	The preliminary recommendations for dexamethasone intravitreal implant include a positive recommendation for people with diabetic macular oedema (DMO) if the implant is to be used in an eye with an intraocular (pseudophakic) lens and non-corticosteroid treatment is unsuitable for them: 1.1 Dexamethasone intravitreal implant is recommended as an option for treating people with diabetic macular oedema only if: • the implant is to be used in an eye with an intraocular(pseudophakic) lens and • their diabetic macular oedema does not respond to non-corticosteroid treatment or such treatment is unsuitable for them. It is unclear what is meant by 'unsuitable'. Section 4.6 of the ACD states that the Appraisal Committee heard from clinical experts that there are no clinical criteria for determining whether a treatment is 'unsuitable' for a person with DMO. Nevertheless, the ACD clearly states in section 4.17 that dexamethasone intravitreal implant was not a cost-effective use of NHS resources compared with laser for treating DMO in people with a pseudophakic lens and a central retinal thickness (CRT) of less than 400 micrometres. This is not clearly reflected in the wording of the guidance	Comment noted. The marketing authorisation for dexamethasone intravitreal implant does not specify what 'unsuitable' means and, as described in the consultation response, the Committee heard from clinical experts that there are no definitive criteria in inform clinical decision-making. No change to the FAD required.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		and 'unsuitable' may be interpreted as not recommended by NICE guidance. We recommend that the definition of 'unsuitable' is clarified in the guidance in Section 1 and reflects the wording of Section 4 of the ACD with regard to the use of dexamethasone intravitreal implant in patients with DMO with a pseudophakic lens and a CRT of under 400 micrometres at baseline.	

The Department of Health submitted a response advising it had no comments.