Response to the appraisal consultation document: Dexamethasone intravitreal implant for treating diabetic macular oedema [ID653]

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Approved name of medicinal product:	Dexamethasone intravitreal implant
Brand name:	Ozurdex®
Company:	Allergan Limited
Date:	11th March 2015

Dear Lori Farrar and Frances Sutcliffe

Allergan welcomes the opportunity to comment on the appraisal consultation document (ACD) for the ongoing single technology appraisal of dexamethasone intravitreal implant (DEX700) for treating diabetic macular oedema (DMO) [ID653]. The ACD recommends DEX700 as an option for treating people with DMO 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.

We would like to confirm that Allergan welcomes the positive draft recommendation within the ACD as it is an important step to making DEX700 available in the UK for a subgroup of DMO patients where current treatment options are limited. However, there remains a significant group of DMO patients who have been identified in the ACD as having a high unmet clinical need but are excluded from this draft recommendation. This is the subgroup which the committee has termed ‘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’. This population represents patients with a natural lens whom either do not respond to, or are not suitable for, non-corticosteroid therapies. The current treatment pathway for these patients is shown in Figure 1 and highlights the lack of available treatment options for this patient population.

At the appraisal committee meeting, there was a constructive discussion focused on the benefit versus risk profile of DEX700 in patients with and without a natural lens and how this translated to some uncertainty in the incremental cost-effectiveness ratios (ICERs), specifically those relating to patients with a natural lens. In addition, it was recognised that other factors, specifically the utility sources used to value health effects within the model and the handling of patient discontinuation, may have contributed to increased uncertainty in the resultant ICERs, upon which the Committee has made its draft recommendation.

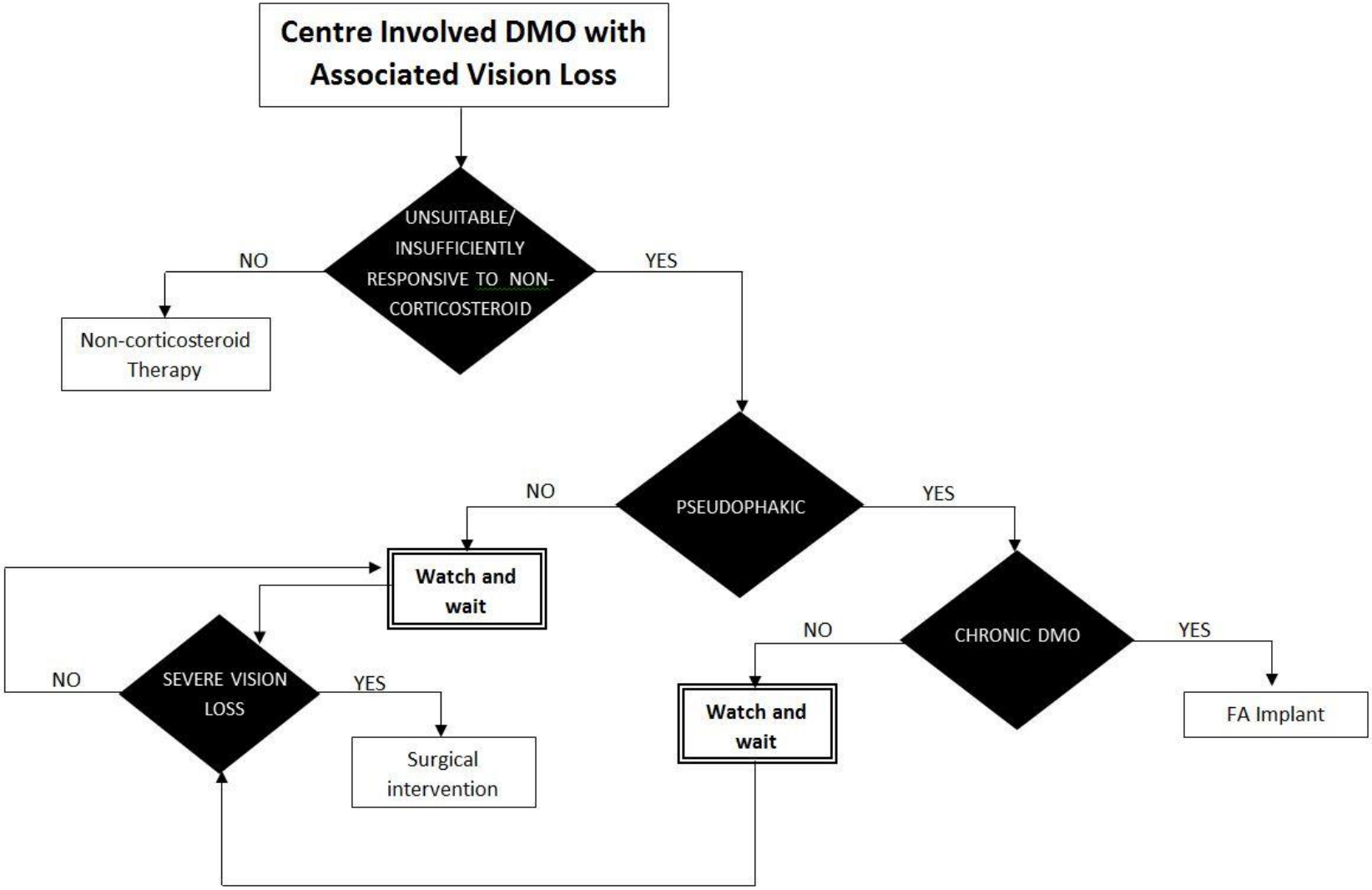
We have recognised the importance of the Committee and ACD feedback and completed additional analyses to further investigate and assess these areas of concern, aiming to reduce the uncertainty in the evaluation of the cost effectiveness of DEX700 in the subgroup of patients with a natural lens who either do not respond to, or are not suitable for, non-corticosteroid therapies. The revised base case analysis in this population is presented in the Appendix to this letter and results in an ICER of £14,978.

NICE specifically requests responses to the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Following a detailed review of the ACD, Allergan would like to address these three points in turn, as well as to provide some additional points of clarification.

Figure 1: Treatment pathway: patients who either do not respond to, or are not suitable for, non-corticosteroid therapies



Key: DMO, diabetic macular oedema; FA, fluocinolone acetonide.

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 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.

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*".

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)*".

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.

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.

In section 3.64 of the ACD it is stated that:

"*The ERG noted that the company did not present data for fluocinolone acetonide 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.

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.

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.

In section 4.8 of the ACD, the Committee noted that:

"*the company had provided subgroup analyses for people with a pseudophakic lens, 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.

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*".

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.

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.

In light of the additional analyses provided here, we ask that the Committee reconsiders its draft recommendation and extends this to include the significant group of DMO patients (those with a natural lens who either do not respond to, or are

not suitable for, non-corticosteroid therapies) who have high unmet clinical need and for whom we strongly believe DEX700 offers a cost-effective treatment option.

We look forward to the resulting discussions at the next Committee meeting on 24 March 2015.

Yours sincerely

Allergan

References

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3. Brown GC, Sharma S, Brown MM, et al. Utility values and age-related macular degeneration. *Arch Ophthalmol*. 2000; 118(1):47-51.
4. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-Year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014; 121(10):1904-14.
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6. Olk RJ. Modified grid argon (blue-green) laser photocoagulation for diffuse diabetic macular edema. *Ophthalmology*. 1986; 93(7):938-50.
7. National Institute for Health and Care Excellence (NICE). TA274: Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). 2013. Available at: http://www.nice.org.uk/guidance/TA274/chapter/1-guidance Accessed: 6 October 2014.