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

Appendix – Additional cost-effectiveness analysis conducted to address uncertainties highlighted in the ACD for patients with a natural lens who either do not respond to, or are not suitable for, non-corticosteroid therapies

Confidential information is highlighted and underlined, e.g. XXXXXX (Academic in confidence) and XXXXXX (Commercial in confidence)

Following the discussions at the appraisal committee meeting and review of the ACD, Allergan has undertaken additional analyses to assess some of the areas of uncertainty highlighted and presented within the ACD. These analyses are of particular relevance to the population of patients with a natural lens whom either do not respond to, or are not suitable for, non-corticosteroid therapies. The Committee in their draft recommendation of DEX700 has not recommended it for this population, which has a high unmet clinical need, as summarised in section 4.19 of the ACD:

"*The Committee noted that, although it preferred using the head-to-head MEAD trial data, the ICER of £1,166,271 per QALY 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 having a higher utility value than the BSE 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.*"

This highlights that a number of factors (utility sources 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 welcome the conclusion of the Committee that the true value of the ICER is likely to be less than the reported £1,166,271 per QALY; and believe that the new analysis presented here (which has an ICER of £14,978) 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 analysis has been conducted using the head-to-head MEAD trial data, which was noted as being preferred by the Committee, and incorporates the corrections made by the ERG in their review of the submitted model. One of the ERG's corrections was to the cost of residential care which they believed should be the cost of private sector residential care instead of the cost of local authority residential care as used in the submitted model. Whilst we recognise that provision is not likely to be 100% local authority residential care, we also believe that it is unlikely that provision will be 100% private sector residential care and that the true cost of residential care is some weighting of the two costs. Therefore the new analysis presented here uses a weighted cost that is 95% of the cost of private sector residential care and 5% of the cost of local authority residential care, giving an annual cost of residential care of £28,985.20. In addition the analysis includes a number of updated modelling assumptions. Three updated assumptions have been included in the new analysis and are described in detail below.

Alternative transition matrices for patients who discontinue from treatment

The Committee noted that the high discontinuation rates in the MEAD studies that led to the sham arm being unrepresentative of patients in clinical practice had likely contributed to the ICER for DEX700 compared with watch–and–wait being overestimated. This is recognised by Allergan as a major limitation of the analysis and a major source of uncertainty in the results upon which the draft recommendation was formulated.

The analysis assessed in the ACD included the assumption that patients who discontinued or were censored from either sham or the DEX700 were assigned transition probability matrices assumed to represent the natural history of vision in patients with DMO, taken from Mitchell *et al*.[1] This assumption was made as the proportions of patients who discontinued or were censored from the studies was non-trivial for both DEX700 and sham, and for these patients, there is no evidence of how their best corrected visual acuity (BCVA) evolved following their removal from the study. The impact of any assumption affects the sham treatment arm more than the DEX700 treatment arm, as a much higher proportion of sham patients discontinued or were censored (56.6%) compared with DEX700 patients (35.9%).[2]

The use of the natural history transition matrix from Mitchell *et al*.[1] is likely to overestimate the BCVA of patients who discontinued due to a lack or loss of efficacy or who were censored from the study, requiring off-protocol treatment. This is due to the fact that the natural history trajectory estimated by Mitchell *et al*.[1] is based on data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[3], which considered a population of patients with diabetes mellitus who may or may not have had an associated ocular condition (e.g. diabetic retinopathy or DMO). Therefore, this may overestimate the level of vision in a population with DMO. Further, the estimate taken from Mitchell *et al*.[1] is based on a total population, and therefore may further overestimate the level of vision in a population who have discontinued treatment, particularly for those who have discontinued due to a lack or loss of efficacy (which is assumed to include those who were censored from the study due to requiring off-protocol therapy). In addition to these limitations, the use of these data does not account for the starting vision as the same probability of improving or worsening vision is applied irrespective of starting health state; this is therefore a crude extrapolation.

A new analysis of the MEAD trial data has been conducted to better examine and approximate the 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. This analysis uses a ‘last transition carried forward’ (LTCF) approach whereby for all patients who discontinued from the study or were censored the last observed transition (i.e. the change in BCVA between the last two visits before discontinuation

or censoring) is applied in every subsequent cycle from the point of discontinuation to the end of the initial 3-year treatment period.

To enable this analysis, transition matrices were generated for each 3-month cycle showing the transitions made by patients who discontinued or were censored from the study during the next 3-month cycle (taking account of the clinical continuation rule described below). These were built up over time to give cumulative LTCF matrices as follows:

- In Cycle 1 (Month 0–3), no discontinuation occurred
- In Cycle 2 (Month 3–6), the transitions from Month 0–3 are applied for those who discontinued between Month 3 and Month 6
- In Cycle 3 (Month 6–9), the transitions from Month 3–6 are applied for those who discontinued between Month 6 and Month 9 **and** the transitions from Month 0–3 are applied for those who discontinued between Month 3 and Month 6
- In Cycle 4 (Month 9–12), the transitions from Month 6–9 are applied for those who discontinued between Month 9 and Month 12 **and** the transitions from Month 3–6 are applied for those who discontinued between Month 6 and Month 9 **and** the transitions from Month 0–3 are applied for those who discontinued between Month 3 and Month 6
- And so on, building the matrices over time

These cumulative LTCF matrices were combined with the observed transition matrices to give an estimated matrix for the total population, assuming no discontinuation from treatment. This methodology has been applied to both the DEX700 and the sham treatment arms and re-treatment rates were adjusted to reflect the lack of discontinuation.

This new analysis allows extrapolation to vary by originating health state and captures the trajectory of change observed at the point of discontinuation in the MEAD trial. Allergan therefore believes this to be a more appropriate approach to modelling the transitions of patients who discontinued or were censored from the MEAD studies than the natural history data (taken from Mitchell *et al*.[1]) which were

used in the main submission and which are not reflective of the expected visual trajectory of these patients.

Incorporation of alternative utility values

The Committee noted that "*the company had not provided any evidence that the utility values used in the model were a good fit to the data nor how the fit would compare with more complex models that allowed interaction between eyes*". The Committee further noted that the narrow bands of utility values from the regression equation derived from the MEAD trial data had likely contributed to the ICER for DEX700 compared with watch–and–wait being overestimated. These are recognised by Allergan as a major limitation of the analysis and a major source of uncertainty in the results from which the draft recommendation was formulated.

A linear regression approach was selected to estimate the associated between VFQ-UI and BCVA from the MEAD trial data. On review of the scatter plots (presented in the appendix 18 of the submission) there was no evidence to suggest that other model types would provide a better fit to the data given the wide spread of responses across the full range of BCVA. Allergan recognises that this is a limitation (due to the observed data rather than method) in the estimation of utilities. An interaction term between BCVA in the best seeing eye and BCVA in the worse seeing eye was included and tested in the models, but offered no model fit improvement and yielded negligible, and clearly non-significant, point estimates for the interaction (details of this were provided in the response to clarification questions document, question B2).

In light of this, published estimates of utilities have been selected for use in place of the utility values derived from the MEAD studies to provide the committee with an overview of the impact of alternative utility values on the results of the analysis. Utility values from Czoski-Murray *et al.*[4] which have a wider range than those derived from the MEAD studies have been preferred by the Committee in other technology appraisals in DMO and have therefore been applied in the additional analyses presented.[5-7] Utility values from Brown[8] and Brown *et al*.[9] have also been included for completeness as these have also been discussed in other technology appraisals in DMO.[5-7]

Czoski-Murray *et al.*[4], Brown[8] and Brown *et al*.[9] report BSE utilities only; therefore the range of utility values in the WSE has been estimated assuming that the change

in the WSE is 30% of the change in the BSE, as per the assumptions made in previous technology appraisals. The utility values reported by Czoski-Murray *et al.*[4], Brown[8] and Brown *et al*.[9] used in the model are summarised in Table 1, Table 2 and Table 3.

Table 1: Czoski-Murray *et al*.[4] utilities

ETDRS letters	Health state in model	BSE utilities reported by Czoski-Murray *et al*. (2009)†	BSE utilities applied in the model	WSE utilities calculated assuming 30% of the change in the BSE	WSE utilities applied in the model
86–100		0.8500		0.8500	
76–85	Health State 6	0.7580	0.8040*	0.8224	0.8362*
66–75	Health State 5	0.6850	0.6850	0.8005	0.8005
56–65	Health State 4	0.6110	0.6110	0.7783	0.7783
46–55	Health State 3	0.5370	0.5370	0.7561	0.7561
36–45	Health State 2	0.4640	0.4640	0.7342	0.7342
26–35	Health State 1	0.3900	0.3715*	0.7120	0.7065*
0–25		0.3530		0.7009	

Key: BSE, better-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study Research Group; WSE, worse-seeing eye.
Notes: *Average of two health states; †Consistent with Table 84 of the ERG report.

Table 2: Brown[8] utilities

ETDRS letters	Health state in model	BSE utilities reported by Brown (1999)†	BSE utilities applied in the model	WSE utilities calculated assuming 30% of the change in the BSE	WSE utilities applied in the model
86–100		0.9200		0.9200	
76–85	Health State 6	0.9200	0.9200*	0.8710	0.8955*
66–75	Health State 5	0.8400	0.8400	0.8470	0.8470
56–65	Health State 4	0.7700	0.7700	0.8260	0.8260
46–55	Health State 3	0.7400	0.7400	0.8170	0.8170
36–45	Health State 2	0.6700	0.6700	0.7960	0.7960
26–35	Health State 1	0.6600	0.6000*	0.7930	0.7750*
0–25		0.5400		0.7570	

Key: BSE, better-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study Research Group; WSE, worse-seeing eye.
Notes: *Average of two health states; †Consistent with Table 84 of the ERG report.

Table 3: Brown *et al*.[9] utilities

ETDRS letters	Health state in model	BSE utilities reported by Brown *et al*. (2000)†	BSE utilities applied in the model	WSE utilities calculated assuming 30% of the change in the BSE	WSE utilities applied in the model
86–100		0.8900		0.8900	
76–85	Health State 6	0.8900	0.8900*	0.8620	0.8760*
66–75	Health State 5	0.8100	0.8100	0.8380	0.8380
56–65	Health State 4	0.5700	0.5700	0.7660	0.7660
46–55	Health State 3	0.5700	0.5700	0.7660	0.7660
36–45	Health State 2	0.5700	0.5700	0.7660	0.7660
26–35	Health State 1	0.5200	0.5200*	0.7510	0.7510*
0–25		0.5200		0.7510	

Key: BSE, better-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study Research Group; WSE, worse-seeing eye.
Notes: *Average of two health states; †Consistent with Table 84 of the ERG report.

The derived utilities for the BSE and WSE across the BCVA-defined health states have been applied within the model as follows.

The distribution of utilities in the BSE across the health states is applied to the distribution of vision across the health states in the baseline-defined BSE and the distribution of utilities in the WSE across the health states is applied to the distribution of vision across the health states in the baseline-defined WSE for all patients. This includes those treated unilaterally in the BSE or WSE and those treated bilaterally. This therefore accounts for the utility associated with the level of vision in both eyes for all patients and remains an improvement upon previous economic modelling that applied the utilities only to the treated eye. This is felt to be important given that the Committee noted in section 4.15 of the ACD that:

"*modelling the transitions for each eye independently was a more realistic approach than that used in previous appraisals of eye conditions, which sometimes modelled the vision in only one eye*".

We believe that the inclusion of these alternative sources of utility values which result in wider ranges of utilities than those derived from the MEAD trial data will reduce the uncertainty around the ICER that has arisen due to this range being narrower than expected.

Incorporation of a clinical continuation rule for DEX700

A pragmatic clinical continuation rule for DEX700 has been applied, whereby patients are assumed not to receive further treatment with DEX700 if they do not achieve a gain of at least 5 letters (i.e. do not respond to treatment) by Month 6 following their first injection of DEX700. This therefore only selects patients for re-treatment who have responded to their first DEX700 injection and are therefore likely to benefit from further treatment with DEX700.

In the MEAD studies, of the 347 patients who were randomised to DEX700, nine had discontinued or were censored prior to the Month 6 visit, leaving 338 patients remaining in the DEX700 treatment arm at Month 6. Of these 338 patients, 105 (31.1%) did not achieve a gain of at least five letters by Month 6 and have therefore been discontinued from treatment with DEX700 within the revised analysis presented here. These patients have been assigned the transition probabilities associated with the natural history of vision, in line with Mitchell *et al*.[1] in the absence of evidence for

the evolution of vision in patients who receive one treatment of DEX700 and are then removed from treatment.

In DMO visual acuity is highly influenced by both oedema of the retina and presence of cataract. As patients with natural lenses can develop cataract, defining a continuation rule to be applied at 6 months, provides the opportunity to identify the patients who will benefit most from continued DEX700 treatment. In order to ensure a positive benefit risk ratio it would be advantageous to see an initial significant improvement in vision in this group of patients. This would not be relevant in pseudophakic patients (with artificial lenses) who cannot develop cataract, and where the stabilization or a modest gain of vision might be a more appropriate goal of treatment and where the treatment has been shown to be cost effective without the application of a clinical continuation rule.

We believe that the inclusion of this clinical continuation rule into the analysis will help to reassure the Committee that if DEX700 is administered to patients with a natural lens who either do not respond to, or are not suitable for, non-corticosteroid therapies and who have demonstrated a clinical benefit (and are therefore considered likely to benefit from further treatment), DEX700 is a cost-effective treatment option in this group of patients.

Results

The results of this analysis are presented in Table 4. The resulting ICER is £14,978, indicating that, under the revised assumptions detailed in this report, DEX700 is considered a cost-effective treatment option compared with watch–and–wait in this population where there is a high unmet clinical need. Probabilistic analysis (5,000 simulations) indicated that DEX700 is cost-effective compared with watch–and–wait at willingness to pay thresholds of £20,000 and £30,000 per QALY gained on 53.96% and 58.42% of occasions. We believe this will reduce the uncertainty the Committee has around the ICER for DEX700 in this patient population, and will give the Committee confidence that the ICER lies within the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained).

Table 4: Revised analysis for patients with a natural lens who either do not respond to, or are not suitable for, non-corticosteroid therapies

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Watch–and–wait	£14,834	6.5400			
DEX700	£17,357	6.7085	£2,523	0.1685	£14,978

Key: DEX700, dexamethasone intravitreal implant; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

To illustrate to the committee the impact of each component of the revised analysis in turn, Table 5 below presents the following scenarios which build up to the revised base case presented in Table 4:

1. ERG corrected base case, provision of residential care 95% private sector and 5% local authority
2. Alternative transition matrices for patients who discontinue from treatment only (using VFQ-UI utilities)
3. Alternative transition matrices for patients who discontinue from treatment using Czoski-Murray *et al*.[4] utilities
4. Alternative transition matrices for patients who discontinue from treatment using Brown[8] utilities
5. Alternative transition matrices for patients who discontinue from treatment using Brown *et al*.[9] utilities
6. Clinical continuation rule only (using VFQ-UI utilities)
7. Clinical continuation rule using Czoski-Murray *et al*.[4] utilities
8. Clinical continuation rule using Brown[8] utilities
9. Clinical continuation rule using Brown *et al*.[9] utilities
10. Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule (using VFQ-UI utilities)
11. Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule using Czoski-Murray *et al*.[4] utilities (revised base case presented in Table 4)

12. Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule using Brown[8] utilities
13. Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule using Brown *et al*.[9] utilities

Table 5: Scenario analysis for patients with a natural lens who either do not respond to, or are not suitable for, non-corticosteroid therapies

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Scenario 1: ERG corrected base case, provision of residential care 95% private sector and 5% local authority					
Watch–and–wait	£10,523	5.7531			
DEX700	£17,276	5.7589	£6,753	0.0058	£1,170,914
Scenario 2: Alternative transition matrices for patients who discontinue from treatment only (using VFQ-UI utilities)					
Watch–and–wait	£14,834	5.6999			
DEX700	£20,388	5.7374	£5,554	0.0374	£148,403
Scenario 3: Alternative transition matrices for patients who discontinue from treatment using Czoski-Murray et al.[4] utilities					
Watch–and–wait	£14,834	6.5400			
DEX700	£20,388	6.6505	£5,554	0.1105	£50,280
Scenario 4: Alternative transition matrices for patients who discontinue from treatment using Brown[8] utilities					
Watch–and–wait	£14,834	7.6180			
DEX700	£20,388	7.7029	£5,554	0.0849	£65,425
Scenario 5: Alternative transition matrices for patients who discontinue from treatment using Brown et al.[9] utilities					
Watch–and–wait	£14,834	6.9741			
DEX700	£20,388	7.0884	£5,554	0.1143	£48,584
Scenario 6: Clinical continuation rule only (using VFQ-UI utilities)					
Watch–and–wait	£10,523	5.7531			
DEX700	£15,870	5.7610	£5,347	0.0079	£678,142
Scenario 7: Clinical continuation rule using Czoski-Murray et al.[4] utilities					
Watch–and–wait	£10,523	6.7096			
DEX700	£15,870	6.7369	£5,347	0.0272	£196,377
Scenario 8: Clinical continuation rule using Brown[8] utilities					
Watch–and–wait	£10,523	7.7470			
DEX700	£15,870	7.7679	£5,347	0.0209	£256,058
Scenario 9: Clinical continuation rule using Brown et al.[9] utilities					
Watch–and–wait	£10,523	7.1149			
DEX700	£15,870	7.1556	£5,347	0.0407	£131,388

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Scenario 10: Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule (using VFQ-UI utilities)					
Watch–and–wait	£14,834	5.6999			
DEX700	£17,357	5.7530	£2,523	0.0530	£47,590
Scenario 11: Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule using Czoski-Murray et al.[4] utilities (revised base case)					
Watch–and–wait	**£14,834**	**6.5400**			
DEX700	**£17,357**	**6.7085**	**£2,523**	**0.1685**	**£14,978**
Scenario 12: Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule using Brown[8] utilities					
Watch–and–wait	£14,834	7.6180			
DEX700	£17,357	7.7462	£2,523	0.1282	£19,683
Scenario 13: Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule using Brown et al.[9] utilities					
Watch–and–wait	£14,834	6.9741			
DEX700	£17,357	7.1396	£2,523	0.1655	£15,252
Key: DEX700, dexamethasone intravitreal implant; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

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