

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Dexamethasone intravitreal implant for
treating diabetic macular oedema**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using dexamethasone intravitreal implant in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Appraisal Committee is interested in receiving comments on 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?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using dexamethasone intravitreal implant in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 12 March 2015 (5pm)

Second Appraisal Committee meeting: 24 March 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

- 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.
- 1.2 People whose treatment with dexamethasone intravitreal implant is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue dexamethasone intravitreal implant until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Dexamethasone intravitreal implant (Ozurdex, Allergan) contains a corticosteroid. It suppresses inflammation and prevents oedema. Dexamethasone intravitreal implant has a marketing authorisation in the UK for 'the treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy'.
- 2.2 Dexamethasone intravitreal implant is given as an injection into the eye. Each implant delivers 700 micrograms dexamethasone to the

back of the eye over a period of 6 months or more. The implant remains in the vitreous for up to 270 days before fully dissolving. The summary of product characteristics states that, after initial treatment, retreatment can be performed after approximately 6 months if the patient experiences decreased vision with or without an increase in retinal thickness with recurrent or worsening diabetic macular oedema. The summary of product characteristics states that patients should be monitored following an injection of dexamethasone intravitreal implant.

- 2.3 The summary of product characteristics includes the following adverse events as common or very common for dexamethasone intravitreal implant: headache, increased intraocular pressure, cataract and conjunctival haemorrhage. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.4 The list price of dexamethasone intravitreal implant is £870.00 per 700 micrograms (excluding VAT; 'British national formulary'; [BNF] accessed online January 2015). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 9) considered evidence submitted by Allergan and a review of this submission by the Evidence Review Group, plus additional analysis (ERG; section 10).

Clinical effectiveness

- 3.1 The company identified 6 randomised controlled trials (RCTs) that compared dexamethasone intravitreal implant with a relevant

comparator in adults with diabetic macular oedema (MEAD-010, MEAD-011, study 024, PLACID, NCT00035906 and BEVORDEX).

3.2 MEAD-010 and MEAD-011 were identical in design and provide the key data for dexamethasone intravitreal implant in the company submission. The trials compared dexamethasone 700 micrograms and dexamethasone 350 micrograms with sham procedure in adults who had been treated before with medical or laser photocoagulation therapy or whose disease was unsuitable for laser photocoagulation therapy. MEAD-010 included 494 patients and took place at 59 study centres in 10 countries, including countries in Australasia, North America, Europe, Asia, and Africa. MEAD-011 included 554 patients and took place at 72 study centres in 14 countries, including countries in South America, Europe, Australasia, Asia and North America. Patients were included in the trials if they had a baseline best corrected visual acuity (BCVA) between 34 and 68 letters and a baseline central retinal thickness (CRT) of 300 micrometres or more. Both trials lasted between 36 and 39 months. In both trials, patients had the first treatment on the day of randomisation. They were evaluated for retreatment at 6 months and then every 3 months, although treatment was not given more often than every 6 months. Patients were eligible for retreatment if retinal thickness in the 1 mm central macular subfield was greater than 225 micrometres (until May 2010) or 175 micrometres (from May 2010), or if optical coherence tomography showed evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening. The primary outcome in both trials was mean BCVA average change from baseline which was performed using analysis of covariance (ANCOVA) with the treatment as a fixed effect and the baseline BCVA as a covariate. For patients with no post-baseline BCVA assessment, the average change from baseline was 0.

- 3.3 Study 024 was an open-label trial comparing dexamethasone 700 micrograms with ranibizumab 0.5 mg. Patients having dexamethasone intravitreal implant were treated at baseline, month 5 and month 10.
- 3.4 PLACID compared dexamethasone 700 micrograms plus laser photocoagulation with sham procedure plus laser photocoagulation in 253 patients. Patients had either dexamethasone intravitreal implant or sham procedure on the day of randomisation. At 1 month, all patients had laser photocoagulation treatment. Patients could have up to 3 additional laser photocoagulation treatments (at months 4, 7 and 10) and 1 additional dexamethasone intravitreal implant treatment or sham procedure (at month 6 or 9).
- 3.5 NCT00035906 compared dexamethasone 700 micrograms and dexamethasone 350 micrograms with observation in 171 patients. The population included people with diabetic macular oedema (DMO) and people with macular oedema associated with uveitis, retinal vein occlusion or Irvine-Gass syndrome, that persisted at least 90 days after laser photocoagulation or medical treatment. Patients had a single treatment at randomisation and were followed for 90 days.
- 3.6 BEVORDEX compared dexamethasone 700 micrograms with bevacizumab 1.25 mg in 88 eyes. Dexamethasone intravitreal implant was not given more than every 4 months.
- 3.7 For full details of the trials, please see the company's submission.

Outcomes of the trials

- 3.8 The outcomes from the trials were analysed using an intention-to-treat approach. Missing data were accounted for by using a last observation carried forward approach.

- 3.9 In the MEAD trials, the pooled results showed there was a statistically significant difference in the mean BCVA average change when dexamethasone intravitreal implant and sham procedure were compared in the general DMO population (3.5 letters with dexamethasone compared with 2.0 letters with sham, $p=0.023$) and in people with a pseudophakic lens (6.5 letters with dexamethasone compared with 1.7 letters with sham, $p<0.001$).

Health-related quality of life

- 3.10 Health-related quality of life and visual functioning were assessed in the MEAD trials. EQ-5D, NEI-VFQ 25 and SF-36 were assessed at baseline and NEI-VFQ 25 was also assessed at follow-up. The NEI-VFQ 25 is a vision-specific quality of life measure that has been validated in a DMO population. It consists of 25 vision-targeted questions that represent 11 vision-related quality-of-life subscales and 1 general health item. SF-36 and EQ-5D were not assessed during follow-up as they do not contain vision-specific items.
- 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, $p=0.89$). The company stated that the health-related quality of life of patients having dexamethasone intravitreal implants was negatively affected by lens opacification and primary cataract formation. A post-hoc

analysis done by the company showed that, after cataract surgery, the improvement in vision-related quality of life associated with dexamethasone intravitreal implant use was greater than that before cataract formation and it was similar to the improvement reported in people with a pseudophakic lens.

Treatments and discontinuations

- 3.12 The mean number of dexamethasone intravitreal implant treatments per patient in the MEAD trials was 4.1. Less than 10% of patients had therapy every 6 months.
- 3.13 In the MEAD trials, 36% of patients in the dexamethasone 700 micrograms group and 57% of patients in the sham procedure group discontinued from the trial. Of the discontinuations in the dexamethasone intravitreal implant group, 36% were because of adverse events, 24% because of 'other' reasons, 18% because of a lack of efficacy, 11% withdrew for personal reasons, 9% were lost to follow-up, and 2% were withdrawn because of protocol violations. Of the discontinuations in the sham group, 42% withdrew because of lack of efficacy, 20% withdrew because of adverse events, 15% withdrew for 'other' reasons, 13% withdrew for personal reasons, 9% were lost to follow up, and less than 1% were withdrawn because of protocol violation. 'Other' reasons included closure of the study site, patient withdrawal of consent, poor compliance from the patient, sponsor request, patient participation in another trial, and patient relocation. In NCT00035906, 7 (12%) of patients in the dexamethasone 700 micrograms group discontinued treatment and 8 (14%) of patients in the observation group discontinued from the trial.

Deaths and adverse events

- 3.14 There were 9 deaths in the dexamethasone intravitreal implant group and 5 deaths in the sham group in the MEAD trials. None of these deaths were related to treatment. There were 2 deaths in the group having dexamethasone intravitreal implant in NCT00035906, although it is not reported whether these were treatment-related deaths, and there were no deaths in the sham group. In the PLACID trial, there were 2 deaths in the dexamethasone intravitreal implant plus laser group and 4 deaths in the laser monotherapy group. None of the deaths were treatment related. The number of deaths study 024 were reported as confidential and cannot be presented here. In PLACID, none of the deaths were treatment related and in study 024 it was not reported whether the deaths were treatment related.
- 3.15 The most common ocular treatment-related adverse events in the MEAD trials were cataract formation and raised intraocular pressure with dexamethasone intravitreal implant, and conjunctival haemorrhage with sham procedure. Treatment was discontinued because of adverse events in 45 (13.0%) of patients having dexamethasone intravitreal implant and 40 (11.4%) of patients having sham in the MEAD trials.
- 3.16 In study 024, the number of treatment-related adverse events was reported as confidential and cannot be presented here.
- 3.17 In PLACID, treatment-related adverse events were reported in 52 (41.6%) eyes treated with dexamethasone intravitreal implant plus laser photocoagulation and in 24 (18.9%) eyes treated with laser photocoagulation alone. There were no serious adverse events related to treatment. The number of treatment-related adverse

events in patients with a pseudophakic lens was not reported in the company's submission.

- 3.18 The number of treatment-related adverse events was not reported for the BEVORDEX or NCT00035906 trials. There were no treatment-related serious adverse events in the dexamethasone intravitreal implant group in NCT00035906.

Subgroup analyses

- 3.19 In patients with a pseudophakic lens, the mean BCVA change from baseline in the MEAD trials was statistically significantly greater with dexamethasone intravitreal implant compared with sham procedure. There were fewer ocular adverse events in the study eye in people with a pseudophakic lens in the MEAD trials than in the general DMO population. This is because people with a pseudophakic lens cannot develop cataracts.

Network meta-analysis

- 3.20 Because the head-to-head trials did not compare dexamethasone intravitreal implant with all of the relevant comparators, the company carried out a network meta-analysis. The network meta-analysis included 5 of the 6 trials already identified (MEAD-010, MEAD-011, study 024, PLACID, and BEVORDEX) plus 6 other RCTs identified in a systematic review carried out specifically for the network meta-analysis (BOLT, ETDRS, OLK, PROTOCOL 1, RESTORE and REVEAL). NCT00035906 was not included in the base-case network meta-analysis because it did not report data at 12 months.
- 3.21 The network meta-analysis included 2 trials that compared dexamethasone intravitreal implant with sham procedure or no treatment (MEAD-010 and MEAD-011). It included 3 trials that compared ranibizumab plus laser photocoagulation with

ranibizumab alone and laser photocoagulation alone (PROTOCOL I, RESTORE, REVEAL) and 2 trials that compared laser photocoagulation with sham or no treatment (ETDRS and OLK). The network also included 1 trial for each of the following comparisons: dexamethasone intravitreal implant compared with ranibizumab (study 024), bevacizumab compared with laser photocoagulation (BOLT), dexamethasone intravitreal implant plus laser photocoagulation compared with laser photocoagulation alone (PLACID), and dexamethasone intravitreal implant compared with bevacizumab (BEVORDEX).

3.22 All trials included in the network meta-analysis reported data for gaining and losing 10 letters at 12 months, except BOLT which only reported data for gaining letters. The network meta-analysis included data for 10-letter loss, a change of less than 10 letters and 10-letter gain for the general DMO population of the trial and for the subgroup of patients who had a pseudophakic lens. The BCVA data from each of the trials were split into the following 3 categories: worsening, defined as a loss of 10 or more letters at 12 months; stable, defined as loss or gain of less than 10 letters at 12 months; and improvement, defined as gain of 10 or more letters at 12 months. The stable vision group for each trial was calculated by subtracting the total number of patients from the number of patients losing 10 or more letters and the number of patients gaining 10 or more letters.

3.23 The incidence of cataracts, raised intraocular pressure (IOP), retinal detachment, endophthalmitis and vitreous haemorrhage from the MEAD-010 (dexamethasone intravitreal implant), MEAD-011 (dexamethasone intravitreal implant), RESTORE (ranibizumab), BOLT (bevacizumab) and PROTOCOL 1 (laser photocoagulation) trials were included in the overall network meta-

analysis for the general DMO population. The adverse events for dexamethasone intravitreal implant and laser photocoagulation were reported as confidential and cannot be presented here. The incidence of raised IOP treated with medication or surgery in year 1 was 0.9% with ranibizumab (RESTORE) and 9.5% with bevacizumab (BOLT). The incidence in all other years was 0.0%. The incidence of retinal detachment, endophthalmitis, and vitreous haemorrhage for ranibizumab and bevacizumab in years 1, 2, and 3 was 0.0%.

3.24 The results of the network meta-analysis for the general DMO population showed that dexamethasone intravitreal implant alone was not associated with a statistically significant benefit in gaining or losing 10 letters over sham or no treatment. The results showed that dexamethasone intravitreal implant plus laser, laser alone, ranibizumab plus laser, ranibizumab alone and bevacizumab were associated with a statistically significantly higher risk of gaining at least 10 letters compared with sham or no treatment and a statistically significantly lower risk of losing at least 10 letters compared with sham or no treatment. The company stated that all models fitted to the general DMO population resulted in mild to moderate heterogeneity between the trials. The company also noted that the 95% credible intervals were wide, denoting uncertainty around the true amount of heterogeneity.

3.25 The company also created a separate network to assess the impact on the efficacy outcomes of patients with a pseudophakic lens at baseline. The network for patients with a pseudophakic lens included the same trials and pathways as the network for the general DMO population, but used data on patients with a pseudophakic lens if available. For trials where data on patients with a pseudophakic lens were not reported separately (OLK,

ETDRS, BOLT, BEVORDEX, REVEAL or RESTORE), the company used general DMO population data. The results of the network meta-analysis for people with a pseudophakic lens were similar to those for the general DMO population. However, dexamethasone intravitreal implant plus laser photocoagulation therapy was not associated with a statistically significantly higher risk of gaining or losing at least 10 letters compared with sham or no treatment (the numbers are reported as confidential and cannot be presented here).

- 3.26 Sensitivity analyses were conducted for the network meta-analysis based on data from the FAME trial, which compared fluocinolone acetonide intravitreal implant with sham procedure. The incidence of cataract in patients without a pseudophakic lens was included in the network meta-analysis (0% in year 1, 66% in year 2 and 42% in year 3). The incidence of raised IOP treated with medication or surgery from FAME was also included in the network meta-analysis (0.0% in year 1, 4.8% in year 2 and 32.3% in year 3). There were no cases of retinal detachment, endophthalmitis, or vitreous haemorrhage from FAME in years 1, 2 and 3. The company reported that the results for all interventions included in the base case remain largely unchanged when FAME trial data were included and when the outcome of gaining 15 or more letters was used. The results of the network meta-analysis including the FAME trial are confidential and cannot be presented here.

Pairwise meta-analysis of the MEAD trials

- 3.27 The company carried out a pairwise meta-analysis of MEAD-010 and MEAD-011 and the results were then qualitatively compared with the results from the network meta-analysis for dexamethasone intravitreal implant compared with sham procedure or no treatment. The results (corrected for an error during the factual error check

stage of the appraisal – see ERG erratum) 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).

Cost effectiveness

- 3.28 The company submitted an economic evaluation that, in the base case, compared dexamethasone intravitreal implant with a watch-and-wait approach for patients with DMO that has not responded to non-corticosteroid treatment or such treatment is unsuitable for them, and compared dexamethasone intravitreal implant with ranibizumab for patients with DMO who have a pseudophakic lens. The company carried out additional analyses comparing dexamethasone intravitreal implant with fluocinolone acetonide intravitreal implant in people with disease that has not responded adequately to non-corticosteroids and laser photocoagulation, and with bevacizumab and watch-and-wait in people with a pseudophakic lens.
- 3.29 For patients with DMO that is considered unsuitable for non-corticosteroid therapy, dexamethasone intravitreal implant was considered as a first- or second-line treatment option. For patients with DMO that has not responded adequately to non-corticosteroid therapy (such as ranibizumab, bevacizumab and laser photocoagulation), dexamethasone intravitreal implant was considered as a second-line treatment. The company considered watch-and-wait to be the most appropriate comparator for patients with disease that has not responded adequately to non-

corticosteroid therapy, and those for whom non-corticosteroid therapy is not suitable. The company used data from the whole DMO population as a proxy for both populations because the available evidence did not suggest a differential efficacy between them and the general DMO population.

- 3.30 For patients with DMO who have a pseudophakic lens, dexamethasone intravitreal implant was considered as a first- or second-line treatment. The company considered the most appropriate comparator to be ranibizumab, as this is the most common first-line treatment for DMO. The analysis was based on the network meta-analysis for patients with a pseudophakic lens. This included data from the subgroup of patients with a pseudophakic lens in the pooled MEAD trials and data for the subgroups of people with a pseudophakic lens in the other trials in the network if available. If data from people with a pseudophakic lens were not available in the trials, data for the whole DMO population were used instead to enable the network to be constructed.
- 3.31 The model had 3-monthly cycles and a time horizon of 15 years. A half-cycle correction and a discount rate of 3.5% for QALYs and costs were applied. An NHS and personal social services perspective was used.
- 3.32 There were 6 health states in the model defined by the BCVA changes in each eye, regardless of whether the eye is treated, in addition to the absorbing health state of death. Both eyes could transition independently between the 6 visual acuity states. The health states were defined by a 10-letter range in BCVA:
- health state 1: people with a BCVA of 35 letters or less
 - health state 2: people with a BCVA of 36–45 letters

- health state 3: people with a BCVA of 46–55 letters
- health state 4: people with a BCVA of 56–65 letters
- health state 5: people with a BCVA of 66–75 letters
- health state 6: people with a BCVA of 76 letters or more.

Patients could move into an improved health state, remain in the same health state, or move into a worse health state. The probability of moving between visual acuity states in each cycle was modelled using transition probability matrices.

- 3.33 The model allowed BCVA changes in both eyes to be modelled independently, with the ‘better-seeing eye’ (BSE) and ‘worse-seeing eye’ (WSE) defined at baseline and fixed throughout the time horizon. The baseline distribution of vision across visual acuity states was reported as confidential and cannot be presented here. Patients entering the model could be affected by DMO in either their BSE or WSE (unilateral DMO), or both eyes (bilateral DMO), with the proportions determined by the pooled number of patients in these groups in the dexamethasone intravitreal implant treatment arms of the MEAD trials. The proportions are assumed to vary by population.
- 3.34 Patients with DMO in 1 eye at baseline could develop DMO in their other eye (‘fellow eye involvement’) and move to bilateral treatment. In the model, this could occur only at the end of year 1 or year 2. Patients with bilateral DMO were assumed to have the same treatment in both eyes. Patients could discontinue treatment because of adverse events or loss of efficacy of treatment.
- 3.35 Patients were at risk of death at all times during the model. The risk of all-cause mortality was applied to all patients, adjusted for the additional mortality from diabetes and from DMO. The model assumed that mortality occurred equally across all visual acuity

states. There was no additional mortality from blindness in the base case (although this was tested in sensitivity analyses).

- 3.36 For the baseline effect, the 3-monthly probabilities of eyes treated with dexamethasone intravitreal implant transitioning between visual acuity states was based on the dexamethasone arm of the pooled MEAD trials. For the relative effect, the transition probabilities for watch-and-wait were calculated by applying the relative risks for sham procedure from the network meta-analysis to the 3-month transition probabilities for dexamethasone intravitreal implant (baseline treatment). For the relative effects of ranibizumab (and bevacizumab, laser photocoagulation and fluocinolone acetonide intravitreal implant in the sensitivity and scenario analyses) the transition probabilities were calculated by applying the relative risks from the network meta-analysis to the 3-month transition probabilities for dexamethasone intravitreal implant (baseline treatment). If treatment was discontinued, visual acuity was assumed to follow the natural history of vision in eyes with DMO. Eyes without DMO were assumed to maintain constant vision.
- 3.37 The model included data for 5 adverse events: cataracts, raised IOP, retinal detachment, endophthalmitis and vitreous haemorrhage. Data were taken from the clinical trials included in the network meta-analysis. Data for watch-and-wait were taken from a natural history study (the Blue Mountains study). The risk of adverse events was assumed to be equal for the general DMO population and the population with a pseudophakic lens, except that there was no risk of cataract in the population with a pseudophakic lens. Adverse effects did not have any effect on health-related quality of life in the model.

- 3.38 The company concluded that the published utility values used within the NICE technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#) and [fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy](#) were subject to a large number of limitations:
- the published utility values corresponded to visual impairment resulting from causes other than DMO
 - the majority of utility values were based on vision in the BSE only, meaning assumptions were needed for the impact of vision resulting from treatment of the WSE or bilateral treatment
 - the health states for which utility values were available did not match the health states in the company's model, meaning adjustments or assumptions were needed to make the published utility data 'fit' within model structures.
- 3.39 Health-related quality of life in the model was dependent on the patient's visual acuity. The company conducted their analyses using Visual Function Questionnaire Utility Index (VFQ-UI) data, which were calculated from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) collected in the MEAD clinical trials. These data related specifically to the DMO population. A regression model was used to estimate utility values for each patient, based on the BCVA of a patient's BSE and WSE. It included vision in the BSE and in the WSE separately as exploratory variables, allowing both eyes to contribute independently to the utility equation used in the economic modelling. The BCVA of the BSE had a higher impact on the estimated utility than the BCVA of the WSE. VFQ-UI data calculated from the VFQ-25 data collected in the MEAD trials were used directly to estimate utilities in the model. EQ-5D values

obtained from the MEAD clinical trials were used in the sensitivity analyses. The company performed a systematic review for publications with additional health-related quality-of-life data, but did not find any relevant studies. The utility values associated with the different visual acuity states are reported as confidential and cannot be presented here.

- 3.40 The company used NHS reference costs and the Monthly Index of Medical Specialities to cost the resources associated with treatment of DMO, including: intervention costs, monitoring and test costs, health state costs and adverse event costs. Treatments were costed as follows: dexamethasone intravitreal implant, £870.00; ranibizumab, £742.17; and fluocinolone acetonide intravitreal implant, £5500. Laser photocoagulation was assumed to have zero cost because all treatment centres were thought to have access to existing equipment. Watch-and-wait was also associated with zero cost. The cost of bevacizumab was assumed to have an acquisition cost of £50.00 in line with the lower limit reported in the NICE Decision Support Unit report on [bevacizumab in eye conditions: issues related to quality, use, efficacy and safety](#). Ranibizumab and fluocinolone acetonide intravitreal implant both have a confidential patient access scheme (PAS) and scenario analyses varying the discount to the list price were provided by the company. The cost of laser photocoagulation administration was assumed to be £116.68. All intravitreal injections were assumed to be given in an outpatient setting at a cost of £116.68. If a day-case procedure was used in the sensitivity analyses, the cost was assumed to be £356.35.
- 3.41 The assumed total costs per round of treatment were different for unilateral and bilateral disease, except for laser photocoagulation which was assumed to have the same cost for both (£116.68). Dexamethasone intravitreal implant was assumed to have a total

cost of £986.68 for treating unilateral disease and £1944.19 for bilateral disease. For ranibizumab, the total cost was £858.85 for unilateral disease and £1659.36 for bilateral disease. The total cost of bevacizumab was £166.68 for unilateral disease and £275.02 for bilateral disease. Fluocinolone acetonide intravitreal implant was assumed to have a total cost of £5616.68 for treating unilateral disease and £11,204.19 for bilateral disease.

3.42 The costs of monitoring and tests used were as follows (all sourced from NHS reference costs): routine monitoring visit, £80.04; optical coherence tomography, £18.06; fluorescein angiography, £116.68; and IOP check, £80.04. The costs of monitoring and treatment were assumed to be equal across all health states. In addition, if BCVA in the BSE fell below 35 letters (severe vision loss), there were a number of additional costs including community care, residential care, hip replacement and depression (total cost per patient per year for severe vision loss is £16,755.23).

3.43 The average number of monitoring visits used in the model was taken from the NICE technology appraisal guidance on [fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy](#) for watch-and-wait and fluocinolone acetonide intravitreal implant, NICE technology appraisal guidance on [ranibizumab for treating diabetic macular oedema \(rapid review of technology appraisal guidance 237\)](#) for ranibizumab, and the summary of product characteristics and clinical opinion for dexamethasone intravitreal implant. In the model it was assumed there would be 4 monitoring visits each year for watch-and-wait, dexamethasone intravitreal implant, and laser photocoagulation. It was assumed there would be 12 visits in year 1, 10 visits in year 2, and 4 visits in year 3 for ranibizumab and bevacizumab.

- 3.44 The average number of treatments per year used in the model was taken from the MEAD trials (dexamethasone intravitreal implant), FAME (fluocinolone acetonide intravitreal implant), RESTORE (ranibizumab), BOLT (bevacizumab, trial data to year 2 and then assumed to be equal to ranibizumab), and PROTOCOL 1 (laser photocoagulation, trial data to year 2 and then the last observation was carried forward). The model assumed a maximum treatment duration of 3 years. The number of treatment visits for dexamethasone intravitreal implant and laser photocoagulation are reported as confidential and cannot be presented here. It was assumed that there would be 1 visit in year 1 and 0.26 visits in years 2 and 3 for fluocinolone acetonide intravitreal implant. The model assumed 7 treatment visits in year 1, 3.9 visits in year 2 and 2.9 visits in year 3 for ranibizumab, and 9 visits in year 1, 4 visits in year 2, and 2.9 visits in year 3 for bevacizumab. It was assumed that there were no treatment visits with watch-and-wait. The model allowed the use of rescue therapy with laser photocoagulation for some interventions, although not in the comparison of dexamethasone intravitreal implant with watch-and-wait.
- 3.45 Adverse events were associated with costs in the model, all taken from NHS reference costs. The cost of a cataract extraction procedure was assumed to be £865.56. The total average cost of treating raised IOP per patient was £262.40 for medical management and £1222.93 for surgical management (costs stated here are those used in the company model). The cost of re-attachment of the retina following retinal detachment was £1685.00. The cost of vitreous biopsy following endophthalmitis was £1393.00. The cost of a vitrectomy procedure following vitreous haemorrhage was £1685.00.

- 3.46 In the company's base case, dexamethasone intravitreal implant dominated watch-and-wait for patients with DMO that does not respond adequately to non-corticosteroid therapy, or such treatment is unsuitable for them (incremental costs: -£1469; incremental quality-adjusted life-years [QALYS] 0.0656). In people with a pseudophakic lens, treatment with ranibizumab resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £50,905 per QALY gained (incremental costs £6004, incremental QALYS 0.1179) compared with dexamethasone intravitreal implant when the list price of ranibizumab was used. The corresponding probabilistic ICER was £89,531 per QALY gained (incremental costs £6710, incremental QALYs 0.0749). When a discount of 50% was applied to the list price of ranibizumab, ranibizumab dominated dexamethasone intravitreal implant in the deterministic analysis (incremental costs -£716, incremental QALYs 0.1179) and probabilistic analysis (incremental costs -£15, incremental QALYs 0.0749).

Company sensitivity analyses and scenarios

- 3.47 The company carried out 1-way sensitivity analyses and scenario analyses to assess the impact on the deterministic results.
- 3.48 In the company's sensitivity analyses for patients with DMO that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them, dexamethasone intravitreal implant remained cost-effective compared with watch-and-wait. The ICERs were most sensitive to changes to the cost of residential care and the percentage of patients requiring residential care.
- 3.49 In the company's sensitivity analyses for people with a pseudophakic lens, dexamethasone intravitreal implant remained

cost effective compared with ranibizumab at list price. The ICERs were most sensitive to changes to the relative risk of worsening vision from the network meta-analysis and the proportion of outpatient procedures for ranibizumab.

- 3.50 The company performed 28 scenario analyses. The scenarios that had a significant impact on the ICER are reported in sections 3.51–3.55.
- 3.51 For patients with DMO that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them, dexamethasone intravitreal implant continued to dominate in the majority of the scenarios. When 1-year and 5-year time horizons were used, dexamethasone intravitreal implant had an ICER of £1,822,946 and £127,034 per QALY gained compared with watch-and-wait. A 10-year time horizon resulted in an ICER of £6365 per QALY gained with dexamethasone intravitreal implant compared with watch-and-wait. Assuming that the person had DMO in their WSE with no fellow eye involvement resulted in an ICER of £131,276 per QALY gained for dexamethasone intravitreal implant compared with watch-and-wait.
- 3.52 For patients with DMO that has not responded adequately to non-corticosteroid therapy, comparison of fluocinolone acetonide intravitreal implant at list price with dexamethasone intravitreal implant resulted in an ICER of £24,591 per QALY gained compared with dexamethasone intravitreal implant. When a discount of 10% was applied to the cost of fluocinolone acetonide intravitreal implant, the ICER was £10,241 per QALY gained compared with dexamethasone intravitreal implant. When a discount of 20% or more was applied to the list price of fluocinolone acetonide intravitreal implant, fluocinolone acetonide intravitreal implant dominated dexamethasone intravitreal implant.

- 3.53 For people with a pseudophakic lens, dexamethasone intravitreal implant was dominated by both laser photocoagulation (incremental costs £7359; incremental QALYs -0.0482) and bevacizumab (incremental costs £6318; incremental QALYs -0.1491).
- 3.54 For people with a pseudophakic lens, the ICERs for ranibizumab compared with dexamethasone intravitreal implant with a 10% and 20% discount to the list price of ranibizumab were £39,510 and £28,116, respectively, per QALY gained. With a discount of 30% and 40% to the list price of ranibizumab, the ICERs were £16,721 and £5327, respectively, per QALY gained. Ranibizumab dominated dexamethasone intravitreal implant when a discount of 50% was applied to the list price of ranibizumab.
- 3.55 For the other scenarios for patients with a pseudophakic lens, a discount of 50% to the list price of ranibizumab was used. Ranibizumab dominated dexamethasone intravitreal implant in most of the scenario analyses. When stable vision after discontinuing treatment was assumed, the ICER was £1554 per QALY gained for ranibizumab. With a 1-year, 5-year and 10-year time horizon the ICERs were £697,936, £47,729 and £7564 respectively per QALY gained. When it was assumed that there was unilateral DMO in the WSE with no fellow eye involvement, the ICER was £57,384 per QALY gained with ranibizumab. When it was assumed that all injections were given as day cases, the ICER was £16,323 per QALY gained, and when it was assumed that 50% of injections were day cases, the ICER was £5128 per QALY gained.

Company response to clarification

- 3.56 The company provided several additional analyses in response to clarification. The key analyses are described below.

- 3.57 In the first analysis, the baseline BCVA distribution in bilateral DMO was taken from the subgroup of patients with bilateral DMO, rather than from patients with unilateral DMO (as in the base case). In people with a pseudophakic lens, the cost effectiveness of dexamethasone intravitreal implant was improved, as it remained cost effective at higher discount to the price of ranibizumab (up to 39% of the list price). Ranibizumab at 50% discount price was not dominant anymore, although it was still cost effective compared with dexamethasone intravitreal implant at an ICER of £7208 per QALY gained.
- 3.58 In the third and fourth analyses, the company used 3-month transition probabilities for both watch-and-wait and dexamethasone intravitreal implant directly from the pooled data from the MEAD trials rather than from the network meta-analysis. The ERG argued that the results of the economic analysis between dexamethasone intravitreal implant and watch-and-wait should be the same, whether the relative effect is taken from the MEAD trials (as in analyses 3 and 4) or from the network meta-analysis (as in the company's base case). However, this is not the case. The ERG argued that this may be because the company used relative risks derived from the network meta-analysis with the assumption that the 12-month relative risks remained constant to year 3. The ERG believed that this assumption was incorrect because the pooled data from the MEAD trials showed that the relative effect of dexamethasone intravitreal implant versus sham procedure is not stable over 3 years. The ERG also argued that the differences in the economic analyses may be a result of the company's normalisation of the transition probabilities which were done so that the probabilities summed up to 1. This may have introduced bias in the company's analysis, although it is not clear how much and in which direction. The company argued that the results of the

network meta-analysis were more appropriate to use than the pooled MEAD data because the sham arm of the MEAD trials was likely to overestimate the true efficacy of a watch-and-wait strategy. 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. In the third analysis, the company restricted movements between health states to a maximum of 1 state (as in the company's base case). This resulted in watch-and-wait dominating dexamethasone intravitreal implant. In the fourth analysis, there was unrestricted movement between health states. This resulted in an ICER of £1,411,676 for dexamethasone intravitreal implant compared with watch-and-wait. The ERG argued that the fourth analysis, which uses data directly from the MEAD trials, appears to be more reflective of relative clinical effects between dexamethasone intravitreal implant versus watch-and-wait for patients with DMO that is unsuitable for or insufficiently responsive to non-corticosteroid therapy.

ERG comments

Clinical evidence

- 3.59 The ERG stated that none of the 6 RCTs of dexamethasone intravitreal implant directly addressed the populations covered by the marketing authorisation. All 6 RCTs included broader populations than those specified in the marketing authorisation.
- 3.60 The ERG stated that none of the RCTs presented in the company's submission directly assessed the efficacy of dexamethasone

intravitreal implant in the populations outlined in the marketing authorisation (people with a pseudophakic lens, and people with DMO that has not responded to non-corticosteroid treatment or such treatment is unsuitable for them). Therefore the efficacy of dexamethasone intravitreal implant in these populations is uncertain, particularly in comparison to the other treatments listed in the final scope. The ERG stated that the whole trial population data should be interpreted with caution in relation to the decision problem. Furthermore, there is an absence of direct comparative data from RCTs comparing the licensed dosing regimen for dexamethasone intravitreal implant with any of the comparators specified by NICE in the decision problem.

- 3.61 The ERG highlighted that study 024 and BEVORDEX used a dosing regimen of dexamethasone intravitreal implant that is not covered in the EU marketing authorisation. The marketing authorisation requires a 6-month waiting period between re-treatments of dexamethasone intravitreal implant, but dexamethasone intravitreal implant was given more frequently than every 6 months in study 024 and BEVORDEX. The ERG argued that these studies are not relevant to the decision problem and did not consider them further in its report.
- 3.62 The ERG highlighted that the 2 MEAD trials and NCT00035906 were 3-armed trials, with 1 of the treatment groups being a lower dose of dexamethasone intravitreal implant than that licensed for use in the UK (350 micrograms). The ERG did not consider data from the trial arm using a lower dose of dexamethasone intravitreal implant to be relevant to the decision problem.
- 3.63 The ERG stated that the treatment algorithms used in the PLACID trial used laser photocoagulation concomitantly with

dexamethasone intravitreal implant, which the ERG did not consider to be in line with UK clinical practice.

- 3.64 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.
- 3.65 The ERG highlighted that the company's submission only reported BCVA outcomes for the study eye, and not for both eyes as requested in the final NICE scope.
- 3.66 The ERG stated that the long-term safety and clinical efficacy data for dexamethasone intravitreal implant is limited because the MEAD trials have a maximum follow-up duration of 39 months.
- 3.67 The ERG stated that the results of the MEAD trials are potentially flawed because of high discontinuation rates across the trial arms (36% in the dexamethasone intravitreal implant arm and 57% in the sham arm) in combination with the use of a last observation carried forward (LOCF) analysis to account for the missing data. The ERG believed that a LOCF approach would only be robust if the disease was stable before people discontinued treatment, and the ERG thought that this was unlikely to be the case in the MEAD trials. The ERG was unable to determine in which direction this bias might affect the results. The ERG was also concerned that the discontinuation rates in the dexamethasone intravitreal implant arm of the MEAD trials were higher than discontinuation rates seen with dexamethasone intravitreal implant in the other RCTs.
- 3.68 The ERG highlighted that the methods used in the network meta-analyses were in line with the methodology recommended by NICE's Decision Support Unit. However, the ERG were concerned

about the validity of the results of the network-meta-analyses for several reasons:

- There were high levels of clinical and statistical heterogeneity in the network meta-analyses, which were partly a result of differences in the baseline characteristics of the studies included in the networks.
- The 95% credible intervals around a large number of the relative risk estimates from the network meta-analyses and the sensitivity analyses were quite wide and thus there is a large amount of uncertainty around the efficacy estimates.
- The frequency of dexamethasone treatments used in the ranibizumab and bevacizumab trials, which differs from that recommended in the European marketing authorisation.
- The trials linking dexamethasone with the other treatments in the network were not considered comparable.
- The poor fit of the models to the datasets (as indicated by the between study standard deviation).

The ERG considered that the results reported from the network meta-analyses should be interpreted with caution.

Cost effectiveness evidence

3.69 The ERG commented that modelling transitions in BCVA states independently for each eye was an improvement over previous economic models assessing treatment for DMO, because it considers the impact of each of the BSE and WSE on HRQOL separately. This allows a more realistic representation of patient experience and a more accurate estimate of health-related quality of life.

3.70 The ERG stated that the model structure appears to be consistent with the progression of the disease and reflective of patient

presentation and treatment in clinical practice. The treatments and populations used in the model were appropriate to inform the decision problem.

- 3.71 The use of the VFQ-UI is more relevant to people with DMO than the EQ-5D because it contains vision-specific items. In addition, the EQ-5D is relatively insensitive to changes in visual functioning.
- 3.72 The ERG highlighted that the data presented by the company in relation to the impact of cataract on health-related quality of life were from a post hoc analysis and were for near-vision rather than for the overall composite NEI-VFQ-25 score, and therefore should be interpreted with caution.

Modelling assumptions and approach

- 3.73 The ERG stated that the economic analysis adopted a number of assumptions and approaches that may have biased the cost effectiveness results, including:
- the assumption that the baseline distributions of BSE and WSE across BCVA states were independent from each other which may have resulted in the WSE being in a better BCVA state than the BSE at baseline, and potentially throughout the duration of the model
 - the assumption that the relative effects of all treatments considered in the network meta-analysis remained stable from initiation of treatment up to 3 years of treatment duration. Evidence from the MEAD trials suggests that this assumption is not correct
 - the ‘normalisation’ of transition probabilities in the economic model, in order to ensure that transition probabilities add up to 1, which resulted in the relative risks from the network meta-analysis being consistently altered from their original values. The

ERG argued that this would have introduced bias into the analysis, although the direction and magnitude of the bias was not clear

- the restriction of transitions between health states for each cycle, so that each patient could only move 1 BCVA health state per cycle. Further analyses requested by the ERG and undertaken by the company showed that this restriction did not reflect the trial evidence.

3.74 The ERG expressed concern that fluocinolone acetonide intravitreal implant was not included in the base case analysis for patients who have a pseudophakic lens and for patients with disease that has not had an adequate response to non-corticosteroid therapy. The ERG was aware, however, that the data analysis needed to include fluocinolone acetonide intravitreal implant in the base case would have considerable limitations.

3.75 The ERG argued that laser photocoagulation should have been included in the base case analysis of patients who have a pseudophakic lens because it is routine clinical practice in patients with DMO and CRT less than 400 microns.

Costs

3.76 The ERG noted that the company may have overestimated the cost associated with severe vision loss (BCVA < 35 letters) because of an overestimation of the cost of residential care. It noted that the company had used the unit cost of residential care provided by a local authority and that this was inconsistent with previous economic analyses in technology appraisals, which used the unit cost of private residential care. It highlighted views that the private sector is the main provider of residential care in the UK. The unit cost of private residential care is almost 50% lower than the unit

cost of residential care provided by a local authority. If the private sector is the main provider of residential care, then use of the unit cost of local authority residential care by the company has greatly overestimated the cost associated with severe vision loss.

Sensitivity analyses

3.77 The ERG stated that the sensitivity analyses conducted by the company were comprehensive. However, the ERG highlighted that the FAME study, used in the company's sensitivity analysis for patients who have not had an adequate response to non-corticosteroid therapy, had 2 major limitations. The study reported the probability of gaining at least 15 letters, meaning that the probability of gaining at least 10 letters had to be estimated for the model. Also, the study only reported 1 of the 3 outcomes of interest (gaining letters) and the remaining 2 outcomes needed to be estimated.

Scenario analyses

3.78 The ERG highlighted that increasing the duration of treatment from 3 to 5 years had no impact on the results in any population. However, they noted that this was because of limitations in the available data, as only 1 maintenance treatment per year (or a maximum of 1 additional fluocinolone acetonide intravitreal implant treatment) was allowed and extrapolation beyond 3 years was based on the LOCF and stable vision in scenarios 5 and 6, respectively. The ERG acknowledged that was unlikely to reflect outcomes in DMO patients observed in clinical practice.

3.79 The ERG did not agree that the scenarios with a time horizon less than 10 years were appropriate, because a short time horizon would not allow the long-term impact of treatment on outcomes to be taken into account. The ERG acknowledged that the company

would have to make a number of assumptions to consider a time horizon of longer than 10 years, because the data were only available for up to 3 years. The ERG noted that increasing the time horizon to 20 years did not have any impact on the results.

- 3.80 The ERG did not believe that giving injections as day cases 100% or 50% of the time was relevant to UK clinical practice because their clinical expert informed them that the vast majority of dexamethasone intravitreal implant and anti-vascular endothelial growth factor (VEGF) treatments, such as ranibizumab and bevacizumab, would be given in an outpatient setting.

ERG corrections to the model

- 3.81 The ERG identified and corrected the following errors in the company's model:
- The annual probability of fellow eye involvement in the model was estimated from the 2 year probability. This is an instantaneous rate and should have been converted to an annual probability.
 - The mean number of re-treatments for fluocinolone acetonide intravitreal implant in year 3 in the model (0.26) was based on LOCF. However, cumulative data for year 3 are available. The number of re-treatments in year 3 was estimated to be 0.036.
 - The probability of cataract for dexamethasone intravitreal implant in years 1, 2, and 3 in the model were 8.40%, 19.17% and 2.94%, respectively. The ERG calculated these as 11.83%, 37.66% and 26.39%, respectively. The annual probability of cataract in people in the watch-and-wait group and in people who discontinued dexamethasone intravitreal implant was also slightly amended from 2.34% to 2.32%.

- The cost of fluorescein angiography in the model was £117, based on the price of a minor vitreous retinal outpatient procedure. The ERG argued this should have been £144 based on the cost of an outpatient ophthalmology contrast fluoroscopy procedure.
- The cost of intermediate vitreous procedures used in the model was £1685. The ERG argued this should have been £989. The ERG argued that the total cost of retinal detachment should have been £1080, because they estimated that the management of retinal detachment was achieved by intermediate vitreous procedure (day case) in 80% of cases and by major vitreous procedure (day case) in 20% of cases.

3.82 The ERG also amended the number of monitoring and treatment visits in the model. As well as correcting the number of treatment visits for fluocinolone acetonide intravitreal implant in year 3 (see section 3.81), it assumed that monitoring visits could incorporate treatment visits for ranibizumab and bevacizumab. The ERG increased the number of treatment visits by 1 for dexamethasone intravitreal implant, fluocinolone acetonide intravitreal implant and laser photocoagulation.

3.83 The ERG's corrections to the model did not change the dominance of dexamethasone intravitreal implant compared with watch-and-wait for all patients with diabetic macular oedema. For people with a pseudophakic lens, ranibizumab remained dominant at a 50% discount to the list price. At list price the ICER for dexamethasone intravitreal implant compared with ranibizumab, when all of the errors were corrected, was £52,494 per QALY gained. Each of the individual corrections resulted in ICERs between £50,849 and £52,494 per QALY gained at the list price of ranibizumab.

ERG scenario analyses

- 3.84 For all patients with DMO, only the change to the unit cost of residential care from local authority price to private price changed the base case ICER. This changed it from dexamethasone intravitreal implant dominating to an ICER of £30,366 per QALY gained for dexamethasone intravitreal implant compared with watch-and-wait.
- 3.85 For people who have a pseudophakic lens, ranibizumab continued to dominate dexamethasone intravitreal implant with a 50% discount to the list price of ranibizumab in all but 2 scenarios – changing the overall mortality hazard ratio and changing the unit cost of residential care. Using an overall mortality hazard ratio of 3.5 for DMO compared with the general population resulted in an ICER of £197 per QALY gained for ranibizumab compared with dexamethasone intravitreal implant. Changing the unit cost of residential care from local authority price to private price resulted in an ICER of £12,889 per QALY gained. When the list price of ranibizumab was used for patients who have a pseudophakic lens, the ICERs for the scenarios ranged from £43,759 to £69,862 per QALY gained.

ERG exploratory ICERs

- 3.86 The ERG's base case ICER incorporated all corrections to errors in the model and included the following scenarios:
- in people with a pseudophakic lens, anti-VEGF treatment in both eyes was assumed to require 1 administration visit 75% of the time and 2 administration visits 25% of the time
 - the numbers of total visits associated with treatment and monitoring of each treatment each year were amended to take

into account that some re-treatment visits included monitoring visits

- costs associated with IOP checks were removed from the analysis, because IOP checks are performed within monitoring visits
- the unit cost of local authority residential care was replaced by the unit cost of private residential care
- updated costs of depression associated with severe vision loss
- the cost of medication for raised IOP was amended to take into account that generic prostaglandins comprise the more widely used pharmacological treatment for raised IOP
- the cost of surgery for raised IOP was amended to take into account that trabeculectomy is the only surgical procedure relevant for raised IOP that is an adverse event of treatment in patients with DMO
- 6 extra IOP visits were assumed for patients with DMO who were treated for raised IOP.

People with a pseudophakic lens with CRT of 400 micrometres or more

3.87 The ICER for patients who have a pseudophakic lens was £63,609 per QALY gained (incremental costs £7378, incremental QALYs 0.1160) for ranibizumab compared with dexamethasone intravitreal implant, when the list price of ranibizumab was used.

3.88 A 10% and 20% discount in the list price of ranibizumab resulted in ICERs of £52,119 and £40,630, respectively, per QALY gained. A 30% and 40% discount resulted in ICERs of £29,141 and £17,651, respectively, per QALY gained. When a 50% discount to the list price of ranibizumab was used, the ICER was £6162 per QALY gained (incremental costs £715, incremental QALYs 0.1160) for ranibizumab compared with dexamethasone intravitreal implant.

People with a pseudophakic lens with CRT less than 400 micrometres

3.89 When laser photocoagulation and bevacizumab were included in the ICER calculation for patients who have a pseudophakic lens, bevacizumab and laser photocoagulation both dominated dexamethasone intravitreal implant.

People who do not have a pseudophakic lens and with diabetic macular oedema that does not respond to non-corticosteroid treatment or such treatment is unsuitable for them

3.90 The ERG's deterministic ICER for dexamethasone intravitreal implant versus watch-and-wait in patients with diabetic macular oedema that does not respond to non-corticosteroid treatment, or such treatment is unsuitable for them, became £22,049 per QALY gained (incremental costs £1428, incremental QALYs 0.0648) when network meta-analysis outputs were utilised; and £1,166,271 per QALY gained (incremental costs £6727, incremental QALYs 0.0058) when data from the MEAD trials for both dexamethasone intravitreal implant and watch-and-wait (sham) were utilised, without transitions being restricted by 1 health state up or down. The ERG emphasised that the results of the model based on the network meta-analyses are characterised by severe flaws including the assumption that relative risks between all treatments of improving vision, stable vision and worsening vision are equal to the 12-month relative risks and are stable over the whole 3-year duration of treatment, and the use of a normalisation approach. The ERG therefore advised that the results obtained from these analyses should be interpreted with great caution.

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

3.91 The ICER for fluocinolone acetonide intravitreal implant compared with dexamethasone intravitreal implant for patients who have a pseudophakic lens and disease that does not respond adequately to non-corticosteroid therapy, or such treatment is not suitable for them, was £45,684 per QALY gained (incremental costs £3569, incremental QALYs 0.0781) when the list price of fluocinolone acetonide intravitreal implant was used. The ICER decreased to £33,047 per QALY gained with a 10% discount in the price of fluocinolone acetonide intravitreal implant, £20,411 per QALY gained with a 20% discount, and £7775 per QALY gained with a 30% discount. With a 40% and 50% discount in the price of fluocinolone acetonide intravitreal implant, it dominated dexamethasone intravitreal implant.

3.92 Full details of all the evidence are in the [Committee papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dexamethasone intravitreal implant, having considered evidence on the nature of diabetic macular oedema and the value placed on the benefits of dexamethasone intravitreal implant by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need and practice

4.1 The Committee heard from patient experts about the nature of diabetic macular oedema (DMO) and their experience with treatment. It heard that the loss of vision has a significant impact on a person's independence; for example, it can affect their ability to drive and perform everyday activities such as dressing and making a cup of tea. The patient experts commented that the condition can disrupt employment because of attendance at regular follow-up or

monitoring appointments and, furthermore, some people may be unable to work or care for family members. The patient experts acknowledged that although an injection into the eye is unpleasant it is not painful, and they are willing to have injections to maintain their sight. They emphasized that the effect of dexamethasone intravitreal implant lasted much longer than anti-VEGF treatments. The Committee heard from clinical experts that although anti-VEGF treatments have made a big difference to clinical practice the need for repeat treatment visits is problematic. The Committee noted that dexamethasone intravitreal implant is licensed for use every 6 months in line with the MEAD trials (see section 3.2) but heard that it is often given more frequently than this in practice (every 4 months). The Committee heard from the clinical and patient experts that there is a clinical need for alternative treatments for people with DMO that is unresponsive to non-corticosteroid treatment. The Committee concluded that patients and clinicians considered dexamethasone intravitreal implant to be a valuable option that could offer longer-term benefits than anti-VEGF treatments to some people with DMO, and for people with DMO that is unresponsive to non-corticosteroid treatment.

- 4.2 The Committee considered which people with DMO would potentially be eligible for treatment with dexamethasone intravitreal implant in clinical practice. The Committee recalled that the indication in the marketing authorisation for dexamethasone intravitreal implant was for the treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy. It noted that this was narrower than the general population with DMO which was enrolled in the clinical trials and specified in the final NICE scope, which was finalised before the marketing

authorisation was granted. The Committee was mindful that it could only make recommendations within the marketing authorisation. It concluded that the 4 potentially eligible populations were:

- People with a pseudophakic lens with CRT of 400 micrometres or more
- People with a pseudophakic lens with CRT less than 400 micrometres
- People who do not have a pseudophakic lens and with diabetic macular oedema that does not respond to non-corticosteroid treatment or such treatment is unsuitable for them
- 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.

4.3 The Committee considered the clinical pathway for people with DMO in relation to the marketing authorisation for dexamethasone intravitreal implant. It heard from the clinical experts that treatment options vary according to the central retinal thickness (CRT), whether their disease is unresponsive to non-corticosteroid treatment and whether such treatment is unsuitable for them, and whether a person has a pseudophakic lens or not.

4.4 The Committee discussed the clinical pathway for people based on CRT levels. For people with a CRT of 400 micrometres or greater, the clinical experts stated that ranibizumab is given as recommended in [ranibizumab for treating diabetic macular oedema](#) (NICE technology appraisal 274). For people who have a CRT of less than 400 micrometres the Committee noted that ranibizumab is not recommended in [ranibizumab for treating diabetic macular oedema](#) (NICE technology appraisal 274) and it heard from clinical

experts that the prescribing options in clinical practice are laser photocoagulation and bevacizumab (outside its marketing authorisation). The Committee heard that bevacizumab was used in some centres and therefore took it into account in its decision-making.

- 4.5 The Committee discussed the clinical pathway for people with DMO that is insufficiently responsive to non-corticosteroid therapy (such as ranibizumab, bevacizumab and laser photocoagulation). The Committee noted that for people who have a pseudophakic lens and chronic disease, fluocinolone acetonide intravitreal implant is recommended in [fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy \(rapid review of technology appraisal guidance 271\)](#) (NICE technology appraisal guidance 301). It heard from the clinical experts that they perceived that fluocinolone acetonide intravitreal implant had been used with caution in the UK because some of its side effects can be difficult to reverse, given its long duration of action. The clinical experts noted that it is given every 36 months, meaning that if IOP becomes elevated (a class effect of intravitreal corticosteroid treatment), then it can be difficult to lower and that surgical intervention might be required. 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’).
- 4.6 The Committee heard from the clinical experts that there are no clinical criteria for determining whether a treatment is unsuitable for a person with DMO; however, they suggested that treatment with an anti-VEGF agent (for example, ranibizumab) is likely to be unsuitable for people who cannot attend monthly appointments,

people who have had a recent cardiovascular event or stroke, or people who have a phobia of needles.

4.7 The Committee considered the most relevant comparators based on the final NICE scope and what it had heard from the clinical experts. The Committee concluded that, based on current practice, the relevant comparators for dexamethasone intravitreal implant in the 4 sub-populations of people with DMO (see section 4.2) are as follows:

- ranibizumab in people with a pseudophakic lens with a CRT of 400 micrometres or greater
- laser photocoagulation or bevacizumab in people with a pseudophakic lens with a CRT less than 400 micrometres
- fluocinolone acetonide intravitreal implant in people with a pseudophakic lens and their chronic DMO does not respond to non-corticosteroid treatment
- watch-and-wait for people who do not have a pseudophakic lens and their DMO does not respond to non-corticosteroid treatment or such treatment is unsuitable for them.

Clinical effectiveness

4.8 The Committee considered the evidence presented by the company on the clinical effectiveness of dexamethasone intravitreal implant. It noted that the main sources of evidence were the MEAD randomised controlled trials, which compared dexamethasone intravitreal implant with sham procedure in a general population of people with DMO (that is, a broader population than that covered by the marketing authorisation). It 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. The

Committee agreed that dexamethasone intravitreal implant resulted in a greater average change in mean best corrected visual acuity (BCVA) than sham procedure for the general DMO population (dexamethasone 3.5 letters vs. sham 2.0 letters, $p=0.023$) and for the subgroup of people with a pseudophakic lens (dexamethasone 6.5 letters vs. sham 1.7 letters, $p<0.001$). The Committee concluded that dexamethasone intravitreal implant is a clinically effective treatment for DMO compared with sham procedure.

- 4.9 The Committee considered the high discontinuation rates in the dexamethasone and sham procedure arms in the MEAD trials. It heard from the clinical experts that the duration of the trials was 3 years which was longer than many other clinical trials in DMO populations; this may have resulted in more people dropping out of the trials. It heard from the company that many people in the sham procedure arm withdrew from the trials because their vision did not improve. In addition, 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. Therefore the people in the sham arm of the MEAD trials are unlikely to be a true representation of the people who would receive watch-and-wait in clinical practice, because in practice people would be less likely to expect an improvement and to seek treatment changes. The ERG noted that people also dropped out of the dexamethasone arm of the trials but to a lesser extent. The Committee accepted that people remaining in the sham arm of the MEAD trials may not be representative of people who would receive dexamethasone intravitreal implant in clinical practice and concluded that the MEAD trials might have underestimated the benefit of dexamethasone intravitreal implant compared with sham procedure.

- 4.10 The Committee considered the evidence for dexamethasone intravitreal implant and its comparators that was derived from the company's network meta-analysis. It noted that evidence from direct comparisons was not available for all comparators, so a network meta-analysis had been carried out by the company. The Committee noted the ERG's concerns that there were high levels of clinical and statistical heterogeneity associated with the network meta-analysis and that there were wide 95% credible intervals around a large number of the relative risk estimates. It further noted that the MEAD trials informed the comparison of dexamethasone intravitreal implant and watch-and-wait and questioned whether a network meta-analysis was necessary when direct trial data were available. The Committee concluded that although the company's network-meta-analysis was associated with uncertainty, it was acceptable to inform its decision-making except for the comparison of dexamethasone intravitreal implant with sham (watch-and-wait). For this comparison, it concluded that its deliberations should be informed by the data from the MEAD trials because they were more robust than the results of the network meta-analysis.
- 4.11 The Committee considered the evidence on adverse events associated with dexamethasone intravitreal implant. It noted that the overall frequency of adverse events in the MEAD trials was acceptable and that there were fewer ocular adverse events in people with a pseudophakic lens compared with the general DMO population. It acknowledged that this was likely to be because cataracts were included as ocular adverse events, and people who have had their lens replaced with a pseudophakic lens cannot develop cataracts. The Committee concluded that dexamethasone intravitreal implant had an acceptable adverse event profile in people with DMO.

Cost effectiveness

4.12 The Committee considered the cost-effectiveness analyses presented by the company and the critique, corrections and exploratory analyses performed by the ERG. The Committee noted that:

- for people with DMO that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them, the company presented a comparison of dexamethasone intravitreal implant with watch-and-wait in its base-case and with fluocinolone acetonide intravitreal implant as a scenario analysis
- 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
- the ERG presented the same comparisons as the company in its exploratory analyses.

The Committee concluded that it had been presented with cost-effectiveness estimates for dexamethasone intravitreal implant in all necessary sub-populations to inform its decision-making.

4.13 The Committee considered the cost of residential care in the company's economic model. The ERG noted that the cost of residential care was overestimated which caused the cost of severe vision loss (BCVA <35 letters) to be overestimated (see section 3.76). This was a key driver in the model for people with DMO that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them. The Committee noted that the company used the cost of local authority care in its model and heard from the ERG that the unit cost of private

residential care should have been used in the model (see section 3.76). The Committee concluded that the costs of severe vision loss had been overestimated in the model.

4.14 The Committee considered the utility values used in the company's model. The Committee noted that the utility values were based on trial data and within a relatively narrow range. The Committee discussed that it was possible that the utility values may have underestimated the disability resulting from the worst health state. It acknowledged 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. However, the Committee noted that published utility values have a number of limitations; in particular, they are not specific to people with DMO (Brown, 1999; Brown et al, 2000; Czoski-Murray et al, 2009). It heard from the ERG that data from the MEAD trials are likely to be more relevant to people with DMO than the published utility values. The Committee acknowledged that the company's approach to inclusion of utility values in the model had some limitations, but so too did the published utility values available. On balance, the Committee concluded that it agreed that the company's utility values were suitable to inform its decision-making, despite these limitations. However, it also concluded that neither approach was ideal and both had shortcomings that inhibited the accurate estimation of the cost effectiveness of dexamethasone intravitreal implant for DMO.

4.15 The Committee considered other elements of the company's model. It acknowledged that the ERG had concerns about several factors that could have biased the results. These included modelling transitions for each eye independently, 'normalising' the transition probabilities in the model to sum them to 1 and assuming

that the relative effect of dexamethasone intravitreal implant compared with sham procedure was stable for 3 years:

- The Committee noted 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. It further noted that the company's approach could result in the worse-seeing eye (WSE) having a better BCVA than the better-seeing eye (BSE).
- The Committee heard that the company's approach to 'normalising' the transition probabilities in the model so that they summed to 1 meant that the relative risks used in the model were different from those provided by the network meta-analysis. The Committee also discussed the assumption in the company's model that movement between health states was restricted to 1 move up or down per cycle. The Committee noted the analyses carried out by the company in response to clarification showed that not restricting the movement between health states had a large impact on the cost-effectiveness results for the comparison of dexamethasone intravitreal implant with watch-and-wait. The Committee heard from the ERG that restricting movements to up or down 1 health state per cycle did not reflect trial evidence from the MEAD trials.
- The Committee also noted that the assumption that the relative effect of dexamethasone intravitreal implant compared with sham was stable for 3 years was not observed in the MEAD trials, which showed that the relative effect was not stable beyond 12 months.

The Committee concluded that these assumptions did not reflect the natural course of the disease nor the observed clinical trial data and that this increased the uncertainty of the results of the model.

People with a pseudophakic lens with CRT of 400 micrometres or more

4.16 The Committee considered the cost effectiveness of dexamethasone intravitreal implant compared with ranibizumab for people who have a pseudophakic lens and a CRT of 400 micrometres or more. It noted that the company's analyses in the pseudophakic population incorporated a range of discounts (from 10% to 50%) applied to the list price of ranibizumab (see sections 3.46 and 3.54). The Committee discussed that in the company's probabilistic base-case analysis using the list price of ranibizumab, the ICER for ranibizumab compared with dexamethasone intravitreal implant was £89,531 per QALY gained. It was aware of the actual discount agreed in the patient access scheme for ranibizumab (the level of the discount for this comparator was agreed with the Department of Health and is commercial in confidence – see [Guide to the processes of technology appraisal](#)), and it agreed that both the analyses undertaken by the company and the ERG captured this discount. Taking into account the exact discount agreed in the patient access scheme for ranibizumab, the Committee concluded that it did not recommend dexamethasone intravitreal implant because it was not a cost-effective use of NHS resources compared with ranibizumab (the most relevant comparator – see section 4.7) for treating DMO in people with a pseudophakic lens and a central retinal thickness of 400 micrometres or more.

People with a pseudophakic lens with CRT less than 400 micrometres

4.17 The Committee considered the cost effectiveness of dexamethasone intravitreal implant compared with laser photocoagulation therapy in people who have a pseudophakic lens and a CRT less than 400 micrometres. It noted that the company's analyses and the ERG's exploratory analyses in the pseudophakic

population (see sections 3.53 and 3.89) showed that dexamethasone intravitreal implant was dominated by laser photocoagulation (that is, laser photocoagulation was less expensive and more effective). The Committee concluded that dexamethasone intravitreal implant was not a cost-effective use of NHS resources compared with laser photocoagulation for treating DMO in people with a pseudophakic lens and a central retinal thickness less than 400 micrometres.

- 4.18 The Committee considered the cost effectiveness of dexamethasone intravitreal implant compared with bevacizumab in people who have a pseudophakic lens and a CRT less than 400 micrometres. It noted that the company's analyses and the ERG's exploratory analyses in the pseudophakic population showed that dexamethasone intravitreal implant was dominated by bevacizumab (that is, it was more costly and less effective than bevacizumab) (see sections 3.53 and 3.89). The Committee concluded that dexamethasone intravitreal implant was not a cost-effective use of NHS resources compared with bevacizumab for treating people with a pseudophakic lens and a central retinal thickness less than 400 micrometres.

People who do not have a pseudophakic lens and with diabetic macular oedema that does not respond to non-corticosteroid treatment or such treatment is unsuitable for them

- 4.19 The Committee considered the cost effectiveness for dexamethasone intravitreal implant compared with watch-and-wait for people who do not have a pseudophakic lens and with DMO that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them. It noted that in the company's base-case analysis dexamethasone intravitreal implant dominated watch-and-wait in people with DMO that does not

respond adequately to non-corticosteroid therapy, or such treatment is unsuitable for them. However the Committee considered the concerns raised by the ERG about the company's model (see section 3.73 and 3.74), acknowledged the ERG's corrections to the company's model (see section 3.81) and noted the ERG's alternative assumptions (see sections 3.82 and 3.86). It noted that in the ERG's exploratory analyses using data directly from the MEAD trials and with unrestricted moves between health states, the ICER was £1,166,271 per QALY gained for dexamethasone intravitreal implant compared with watch-and-wait. It noted that in the ERG's exploratory analyses using data from the network meta-analysis and with restricted moves between health states, the ICER was £22,049 per QALY gained for dexamethasone intravitreal implant compared with watch-and-wait. The Committee was mindful of its earlier conclusion that trial data from the MEAD trials were more robust than the results of the network meta-analyses for the comparison of dexamethasone intravitreal implant with watch-and-wait (see section 4.10) because of the reliance of the network meta-analysis on assumptions that did not reflect clinical practice. 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.

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

4.20 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 noted that the company's and the ERG's analyses incorporated a range of discounts (from 10% to 50%) applied to the list price of fluocinolone acetonide intravitreal implant (see sections 3.52 and 3.91). The Committee was aware of the actual discount agreed in the patient access scheme for fluocinolone acetonide intravitreal implant (the level of the discount for this comparator was agreed with the Department of Health and is commercial in confidence – see [Guide to the processes of technology appraisal](#)) and it agreed that the analyses undertaken by both the company and the ERG captured this discount. The Committee noted that when the exact discount agreed in the patient access scheme for fluocinolone acetonide intravitreal implant was taken into account, there was little difference in the total costs and total QALYs of fluocinolone acetonide intravitreal implant and dexamethasone intravitreal implant. Therefore, it considered that the cost effectiveness of dexamethasone intravitreal implant is likely to be similar to

fluocinolone acetonide intravitreal implant. The Committee considered that, on balance, dexamethasone intravitreal implant would provide an alternative treatment option to fluocinolone acetonide intravitreal implant. The Committee concluded that dexamethasone intravitreal implant was a cost-effective use of NHS resources and recommended it as a treatment option for treating DMO in people who have a pseudophakic lens **and** whose DMO has not responded adequately to non-corticosteroid therapy, or such treatment is not suitable for them.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title: Dexamethasone intravitreal implant for treating diabetic macular oedema	Section
Key conclusion		
<p>Dexamethasone intravitreal implant is recommended as an option for treating people with diabetic macular oedema only if:</p> <ul style="list-style-type: none"> • 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. <p>Because it considered that the cost effectiveness of dexamethasone intravitreal implant was likely to be similar to fluocinolone acetonide intravitreal implant when the patient access scheme for fluocinolone intravitreal implant is applied, the Committee recommended dexamethasone intravitreal implant as a treatment option for treating DMO in people who have a pseudophakic lens and whose DMO has not responded adequately to non-corticosteroid therapy, or such treatment is not suitable for them.</p> <p>The Committee noted that the ICERs for dexamethasone intravitreal implant compared with ranibizumab that incorporated the ranibuzimab patient access scheme in people with a pseudophakic lens and a central retinal thickness of 400 micrometres or more did not fall within the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained) and concluded that dexamethasone intravitreal implant was not a cost-effective use of NHS resources in this patient group.</p> <p>The Committee noted that dexamethasone intravitreal implant was dominated by laser photocoagulation and bevacizumab in people with a</p>		<p>1.1 4.16– 4.20</p>

<p>pseudophakic lens and a central retinal thickness less than 400 micrometres (that is, dexamethasone intravitreal implant was less effective and more costly) and concluded that it was not a cost-effective use of NHS resources in this patient group.</p> <p>The Committee considered the ICERs for dexamethasone intravitreal implant compared with watch-and-wait in people who do not have a pseudophakic lens and who have diabetic macular oedema that has not responded adequately to non-corticosteroid therapy, or such treatment is unsuitable for them. It preferred the ERG's ICER of £1,166,271 per QALY gained because this used head-to-head trial data rather than results from the network meta-analysis but acknowledged that the true value of the ICER was likely to be less than this. However, it considered that it was extremely unlikely that the ICER would be within the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained).</p>		
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from the clinical experts that for people with a CRT of 400 micrometres or greater, ranibizumab is given as recommended in ranibizumab for treating diabetic macular oedema (NICE technology appraisal 274). For people who have a CRT of less than 400 micrometres the Committee noted that ranibizumab is not recommended in ranibizumab for treating diabetic macular oedema (NICE technology appraisal guidance 274) and it heard from clinical experts that the prescribing options in clinical practice are laser photocoagulation and bevacizumab (outside its marketing authorisation).</p> <p>The Committee acknowledged that for people who have a pseudophakic lens and chronic disease which has not responded to prior therapy, fluocinolone acetonide intravitreal implant is recommended in fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271) (NICE technology appraisal guidance 301).It heard from the clinical experts that they perceived that fluocinolone intravitreal implant had been used with caution in the UK because some of its side effects can be difficult to reverse, given its long duration of action.</p> <p>The Committee heard from the clinical experts that people with DMO who do not have a pseudophakic lens are monitored but do not have</p>	<p>4.4-4.6</p>

	<p>active treatment (also known as ‘watch– and– wait’).</p> <p>The Committee heard from the clinical experts that there are no clinical criteria for determining whether a treatment is unsuitable for a person with DMO; however, they suggested that treatment with an anti-VEGF agent (for example, ranibizumab) is likely to be unsuitable for people who cannot attend monthly appointments, people who have had a recent cardiovascular event or stroke, or people who have a phobia of needles.</p>	
The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee concluded that patients and clinicians considered dexamethasone intravitreal implant to be a valuable option that could offer longer-term benefits than anti-VEGF treatments to some people with DMO, and for people with DMO that is unresponsive to non-corticosteroid treatment.</p> <p>The company did not make any claim for innovation.</p>	<p>4.1</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee recalled that the indication in the marketing authorisation for dexamethasone intravitreal implant was for the treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy and was mindful that it could only make recommendations within the marketing authorisation. It concluded that the 4 potentially eligible populations were:</p> <ul style="list-style-type: none"> • People with a pseudophakic lens with CRT of 400 micrometres or more • People with a pseudophakic lens with CRT less than 400 micrometres • People who do not have a pseudophakic lens and with diabetic macular oedema that does not respond to non-corticosteroid treatment or such treatment is unsuitable for them • 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. 	<p>2.1 4.2</p>
<p>Adverse reactions</p>	<p>The Committee concluded that dexamethasone intravitreal implant had an acceptable adverse event profile in people with DMO.</p>	<p>4.11</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The Committee accepted that the high discontinuation rates in the MEAD trials may have underestimated the benefit of dexamethasone intravitreal implant compared with sham procedure.</p> <p>The Committee concluded that the trial data from the MEAD trials were more robust than the results of the network meta-analysis for the comparison of dexamethasone intravitreal implant and sham procedure (watch-and-wait).</p>	<p>4.9 4.10</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee heard from the clinical and patient experts that dexamethasone intravitreal implants last much longer than anti-VEGF treatments, and that the need for repeat treatment visits with anti-VEGFs can be problematic.</p>	<p>4.1</p>

<p>Uncertainties generated by the evidence</p>	<p>The Committee accepted that the high discontinuation rates in the MEAD trials may have underestimated the benefit of dexamethasone intravitreal implant compared with sham procedure.</p> <p>The Committee concluded that the data from the MEAD trials were more robust than the results of the network meta-analysis for the comparison of dexamethasone intravitreal implant and sham procedure (watch-and-wait).</p>	<p>4.9 4.10</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>Not applicable.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>On the basis of the MEAD trials, the Committee concluded that dexamethasone intravitreal implant is proven to be an effective treatment compared with sham procedure in people with diabetic macular oedema.</p>	<p>4.8</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The Committee concluded that it had been presented with cost-effectiveness estimates for dexamethasone intravitreal implant in all necessary sub-populations to inform its decision-making.</p>	<p>4.12</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee concluded that the costs of severe vision loss had been overestimated in the company's model by using local authority costs rather than private costs for residential care.</p> <p>The Committee acknowledged the ERG's concerns about several factors that could have biased the results, including modelling transitions for each eye independently, 'normalising' the transition probabilities in the model to sum them to 1 and assuming that the relative effect of dexamethasone intravitreal implant compared with sham procedure was stable for 3 years. The Committee concluded that these assumptions did not reflect the natural course of the disease or the observed clinical trial data and that this increased the uncertainty of the results of the model.</p>	<p>4.13 4.15</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee noted that the utility values used in the company's model were based on trial data. It acknowledged that the company's approach to inclusion of utility values in the model had some limitations, but so too did the published utility values available. On balance, the Committee concluded that neither approach was ideal, but it agreed that it agreed that the company's utility values were suitable to inform its decision-making, despite these limitations. However, it also concluded that neither approach was ideal and both had shortcomings that inhibited the accurate estimation of the cost effectiveness of dexamethasone intravitreal implant for DMO.</p>	<p>4.14</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Not applicable.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>For people with diabetic macular oedema that has not responded adequately to non-corticosteroid therapy or such treatment is unsuitable for them, the key driver of cost effectiveness in the model is the cost of residential care used for people with severe vision loss.</p>	<p>4.13</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>For people with a pseudophakic lens with CRT of 400 micrometres or more, the Committee concluded that if the confidential patient access scheme for ranibizumab was included, it did not recommend dexamethasone intravitreal implant because it was not a cost-effective use of NHS resources compared with ranibizumab.</p> <p>For people with a pseudophakic lens with CRT less than 400 micrometres, the Committee noted that dexamethasone intravitreal implant was dominated by laser photocoagulation therapy and bevacizumab.</p> <p>For people without a pseudophakic lens with diabetic macular oedema that is unsuitable for or insufficiently responsive to non-corticosteroid therapy, 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</p>	<p>4.16– 4.20</p>

	gained). For people with a pseudophakic lens with diabetic macular oedema that is unsuitable for or insufficiently responsive to non-corticosteroid therapy the Committee noted that, when the exact discount agreed in the patient access scheme for fluocinolone acetonide intravitreal implant was taken into account, there was little difference in the total costs and total QALYs of fluocinolone acetonide intravitreal implant and dexamethasone intravitreal implant. Therefore, it considered that the cost effectiveness of dexamethasone intravitreal implant is likely to be similar to fluocinolone acetonide intravitreal implant.	
Additional factors taken into account		
Patient access schemes (PPRS)	A patient access scheme is in place for 2 of the comparators – ranibizumab and fluocinolone acetonide intravitreal implant. These are taken into account in the Committee’s conclusions.	4.16, 4.20
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No issues relating to equality considerations were raised in the submissions, or in the Committee meeting.	

5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraph

above. This means that, if a patient has diabetic macular oedema and the doctor responsible for their care thinks that dexamethasone intravitreal implant is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy \(rapid review of technology appraisal guidance 271\)](#). NICE technology appraisal guidance 301. 2013.
- [Ranibizumab for treating diabetic macular oedema \(rapid review of technology appraisal guidance 237\)](#). NICE technology appraisal guidance 274. 2013.

- [Preventing type 2 diabetes: risk identification and interventions for individuals at high risk](#). NICE public health guidance 38. 2012.
- [Preventing type 2 diabetes: population and community-level interventions](#). NICE public health guidance 35. 2011.
- [Type 2 diabetes: The management of type 2 diabetes](#). NICE clinical guideline 87. 2009.
- [Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults](#). NICE clinical guideline 15. 2004.

Under development

- Type 1 diabetes in adults. NICE clinical guideline, publication expected August 2015.
- Type 2 diabetes in adults. NICE clinical guideline, publication expected August 2015.
- Afibercept for treating diabetic macular oedema. NICE technology appraisal guidance, publication expected June 2015.

7 Proposed date for review of guidance

- 7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
February 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

David Chandler

Lay Member

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Professor Wasim Hanif

Professor in Diabetes and Endocrinology, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Emily Lam

Lay Member

Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Dr Patrick McKiernan

Consultant Paediatrician, Birmingham Children's Hospital

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Suzanne Martin

Reader in Health Sciences

Dr Iain Miller

Founder & CEO, Health Strategies Group

Dr Paul Miller

Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

Dr Judith Wardle
Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ella Fields

Technical Lead

Fay McCracken

Technical Adviser

Lori Farrar

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Group:

- Edwards SJ, Wakefield V, Mavranetzouli I, Karner C, Marceniuk G, Azuara-Blanco A. Dexamethasone intravitreal implant for diabetic macular oedema : A Single Technology Appraisal. BMJ-TAG, 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Allergan

II. Professional/expert and patient/carer groups:

- Diabetes UK
- Fight for Sight
- Macular Society
- Royal National Institute of Blind People (RNIB)
- Royal College of Ophthalmologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Alimera
- Novartis Pharmaceuticals
- MRC Clinical Trials Unit
- BMJ Group
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Dexamethasone intravitreal implant for treating diabetic macular oedema by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Ian Pearce, Consultant Ophthalmologist, nominated by The Royal College of Ophthalmologists, endorsed by RNIB, Macular Society and Diabetes UK – clinical expert
- Sobha Sivaprasad, Consultant ophthalmologist, nominated by Allergan – clinical expert
- Clara Eaglen, Policy and Campaigns Manager, nominated by RNIB – patient expert
- Gary Forrest, nominated by RNIB – patient expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Allergan