NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Dexamethasone intravitreal implant for treating diabetic macular oedema

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical evidence

- How generalizable are the results from the randomised trials for the general diabetic macular oedema (DMO) population to the DMO sub-populations specified in the marketing authorisation for dexamethasone intravitreal implant?
  - Dexamethasone intravitreal implant is licensed 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'. This is a narrower indication than originally anticipated by the company.
  - The populations in the randomised controlled trials of dexamethasone intravitreal implant included the general population of people with diabetic

macular oedema (DMO), which is a broader population than the population specified in the marketing authorisation.

- Are the trials using different dosing regimens to those approved for use in the UK relevant to the decision problem?
  - There are no direct comparative data from randomised controlled trials comparing the licensed dosing regimen of dexamethasone intravitreal implant with all of the comparators stated in the decision problem.
- Are the outcomes reported appropriate for making recommendations on the specific DMO populations in the marketing authorisation for dexamethasone intravitreal implant?
  - Data on all outcomes listed in the final scope are not reported for some of the comparators and MA populations.
- Are the data from the MEAD studies robust enough to make recommendations on the use of dexamethasone intravitreal implant in patients with DMO?
  - There were high discontinuation rates in the studies that provide the key data for dexamethasone intravitreal implant (the MEAD trials) (36% in the dexamethasone arms and 57% in the sham arms) but the ERG was unable to determine the direction or size of the potential bias that may result.
- Is it appropriate to use data from the MEAD trials to assess the long term clinical effectiveness and safety of dexamethasone intravitreal implant?
  - There are limited long term clinical and safety data for dexamethasone intravitreal implant. The data in the MEAD trials were limited to a maximum of 39 months (3 years and 3 months), which was the maximum length of the trials.
- Are the results of the network meta-analysis valid and appropriate for use in the economic analysis?
  - The network meta-analysis used for the indirect comparison had high levels of clinical and statistical heterogeneity and the ERG noted that the model chosen was a poor fit for the underlying data.
  - The ERG also noted that the 95% credible intervals were wide, denoting uncertainty around the true amount of heterogeneity.

Cost-effectiveness evidence

- Which comparator or comparators are the most appropriate for patients with diabetic macular oedema (DMO)? Should fluocinolone acetonide have been included as a comparator in the base case analysis for patients who have a pseudophakic lens and for patients who are insufficiently responsive to non-corticosteroid therapy? Should laser photocoagulation have been included as a comparator in the base case analysis for pseudophakic patients?
  - The company included ranibizumab as the only comparator for pseudophakic patients in their base case analysis and presented a scenario analysis that included laser photocoagulation, bevacizumab and watch and wait as additional comparators.
  - The ERG argued that fluocinolone acetonide should have been included in the base case analysis for patients who have a pseudophakic lens and for those who are insufficiently responsive to non-corticosteroid therapy, although they acknowledged that the data analysis would have considerable limitations.
  - The ERG also argued that laser photocoagulation should have been included in the base case analysis for patients who have a pseudophakic lens as it is routine clinical practice in patients with a CRT less than 400 microns.
- Is the assumption in the company's model that the baseline distributions of better seeing eye (BSE) and worse seeing eye (WSE) were independent of each other reasonable?
  - This assumption may have resulted in the WSE being in a better best corrected visual acuity (BCVA) state than the BSE at baseline, and potentially throughout the duration of the model.
- Is it appropriate to assume that the relative effect of all treatments considered in the network meta-analysis would remain stable for up to 3 years for the whole population? And is it appropriate for patients with a pseudophakic lens?
  - Evidence from the MEAD trials suggests that this may not be the correct assumption in the whole population.
- Are the relative risks used in the model accurate?
  - The transition probabilities used in the company's model have been 'normalised' in order to add up to 1.

  - This altered the relative risks used in the model from the original relative risks obtained from the network meta-analysis.
  - The direction and size of the bias caused by this is unknown.
- Are the restrictions on the transitions between health states in the model appropriate?
  - The company's model restricted transitions between health states to a maximum of one BCVA state per cycle, which does not reflect trial evidence.
- Is it more appropriate to use the price of local authority care or private care for the unit cost of residential care in the estimate of the cost of severe vision loss?
  - The cost of residential care was overestimated in the company's model, which caused the cost of severe vision loss (i.e. BCVA <35 letters) to be overestimated.
  - The ERG's scenario analyses also showed that when the unit cost of residential care was changed from local authority price to private price the base case ICER for dexamethasone intravitreal implant compared with watch and wait changed from dexamethasone intravitreal implant dominating to £30,366 per QALY gained.
  - The unit cost of residential care was one of the key drivers in the model.
- Are the number of monitoring and treatment visits suggested by the ERG appropriate for ranibizumab?
  - The frequency of monitoring requirements in the summary of product characteristics (SmPC) for ranibizumab have recently been revised from 'monthly' to 'as needed'.

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of dexamethasone intravitreal implant within its licensed indication for treating diabetic macular oedema.

1.2 The decision problem for this appraisal is outlined in table 1.

Table 1. Decision problem [adapted from table on page 80 of company's submission]

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with diabetic macular oedema	Adult patients with visual impairment due to DMO, who have a pseudophakic lens, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy	In accordance with EU licence terms for the use of dexamethasone intravitreal implant in DMO.	None of the populations in the 6 RCTs directly addressed the populations covered by the marketing authorisation – they all had broader populations.
Int.	Dexamethasone intravitreal implant, alone or in combination with laser photocoagulation	Dexamethasone intravitreal implant, alone or in combination with laser photocoagulation	None	2 of the RCTs used treatment regimens not approved for use in the UK – retreatment was allowed more frequently than 6 months (BEVORDEX and study 024).
Com.	• Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: • Ranibizumab • Fluocinolone acetonide intravitreal implant • Bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable)	• Laser photocoagulation alone (for people who have a pseudophakic lens) The following technologies alone or in combination with laser photocoagulation: • Ranibizumab (for people have a pseudophakic lens) • Fluocinolone acetonide intravitreal implant (for people who are considered insufficiently responsive to non-corticosteroid therapy) • Bevacizumab (for people who have a pseudophakic lens and in whom ranibizumab and fluocinolone	In accordance with EU licence terms for the use of dexamethasone intravitreal implant in DMO.	The company used a network meta-analysis to provide data for some of the comparators where there were no head-to-head studies. The ERG had concerns over the validity of the results of the network meta-analysis because of clinical and statistical heterogeneity. The ERG were concerned that for people with a pseudophakic lens, fluocinolone acetonide was not considered as a comparator and laser photocoagulation was only included in a scenario analysis.

		acetonide implants are unsuitable) • Watch and wait (for people who are considered unsuitable for non-corticosteroid therapy and for people who are considered insufficiently responsive to non-corticosteroid therapy in whom the fluocinolone acetonide implant is unsuitable)		
Out.	• Best corrected visual acuity (the affected eye) • Best corrected visual acuity (both eyes) • Central foveal subfield thickness • Contrast sensitivity • Mortality • Need for cataract surgery • Adverse effects of treatment (including cataract formation and glaucoma) • Health-related quality of life, including the effects of changes in visual acuity.	• Best corrected visual acuity (the affected eye) • Best corrected visual acuity (both eyes) • Central foveal subfield thickness • Contrast sensitivity • Mortality • Need for cataract surgery • Adverse effects of treatment (including cataract formation and glaucoma) • Health-related quality of life, including the effects of changes in visual acuity.	None	Data for BCVA for both eyes was not specifically reported in any of the studies. Not all outcomes were included in any of the dexamethasone intravitreal implant RCTs or in all of the trials in the network meta-analysis.

Abbreviations: BCVA, best corrected visual acuity; Com., comparators; DMO, diabetic macular oedema; Int., interventions; Out., outcomes; Pop., population.

2 The technology and the treatment pathway

2.1 Dexamethasone injectable intravitreal implant delivers 700µg dexamethasone to the posterior segment of the eye through a solid polymer drug delivery system over a period of 6 months or more. The implant remains in the vitreous for up to 270 days before fully dissolving. Intravitreal injection is a common ocular procedure within the NHS and is performed routinely as an outpatient procedure. Dexamethasone intravitreal implant is licensed 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 The existing treatment options for diabetic macular oedema (DMO) are laser photocoagulation, Vascular Endothelial Growth Factor (VEGF) inhibitors (ranibizumab, bevacizumab), and fluocinolone acetonide. NICE technology appraisal guidance 274 recommends ranibizumab as an option for treating visual impairment due to DMO (only if the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and the manufacturer provides ranibizumab with the discount agreed in the patient access scheme). NICE technology appraisal guidance 301 recommends fluocinolone acetonide intravitreal implant for treating chronic DMO that is insufficiently responsive to available therapies (only if the implant is to be used in an eye with an intraocular pseudophakic lens and the manufacturer provides fluocinolone acetonide with the discount agreed in the patient access scheme). Bevacizumab is also used outside its marketing authorisation for treating DMO. Details on the technologies included in this appraisal are presented in table 2.

2.3 The marketing authorisation for dexamethasone intravitreal implant covers three groups of people with visual impairment due to DMO:

- those whose disease is unsuitable for non-corticosteroid therapy

- those whose disease is insufficiently responsive to non-corticosteroid therapy
- those with a pseudophakic lens.

2.4 The treatment pathway for patients with DMO and the company's anticipated position for dexamethasone intravitreal implant is shown in figure 1. The company anticipates that dexamethasone intravitreal implant would be used in people who are unsuitable for non-corticosteroids (for which there are no existing treatment options); people who are phakic (that is, who do not have a pseudophakic lens) and do not have a sufficient response to bevacizumab, ranibizumab or laser (instead of retreatment with bevacizumab, ranibizumab or laser photocoagulation); and people who have a pseudophakic lens (instead of bevacizumab, ranibizumab or laser photocoagulation).

Figure 1. Treatment pathway for patients with diabetic macular oedema, including dexamethasone intravitreal implant [figure 3 in company's submission]

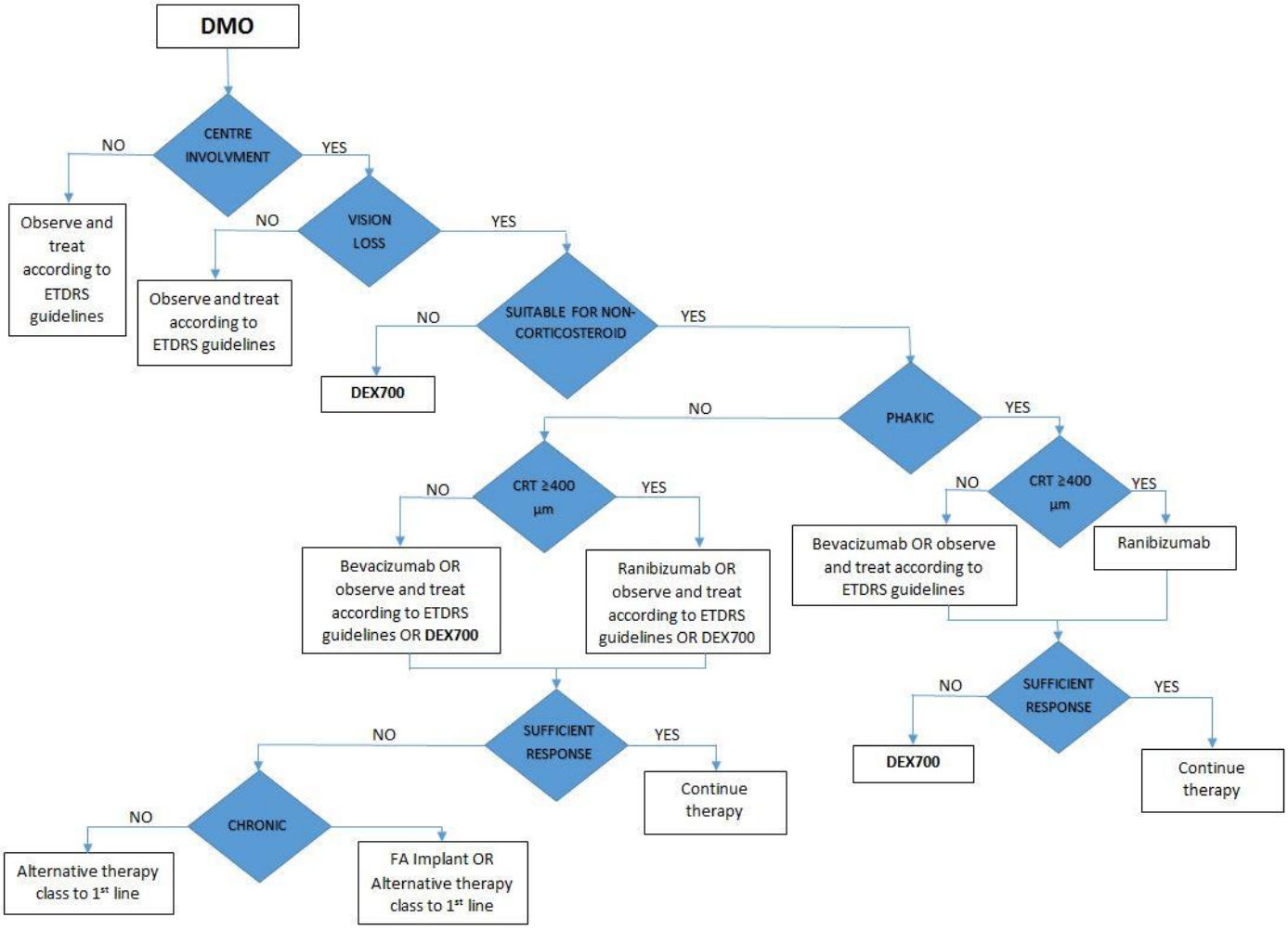

Table 2. Technologies [adapted from SmPCs and table 103 on page 402 of company's submission]

	Marketing authorisation	Administration method	Costs used in the company's submission
Dexamethasone intravitreal implant	Treatment of adult patients with visual impairment due to diabetic macular oedema who have a pseudophakic lens or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.	Intravitreal injection Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs.	List price: £870.00 per applicator (excl. VAT)
Laser photocoagulation	Laser photocoagulation is a type of surgery and therefore does not require a marketing authorisation.	Laser	Acquisition cost: £0 (all facilities are thought to have access to existing equipment to perform laser procedures)
Ranibizumab	Treatment of visual impairment due to diabetic macular oedema in adults.	Intravitreal injection Monitoring should be determined by the physician based on disease activity.	List price: £742.17 per vial (excl. VAT). There is a patient access scheme in place for ranibizumab.
Fluocinolone acetonide intravitreal implant	Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.	Intravitreal injection Patients should be monitored within 2 to 7 days following the procedure for potential complications. It is recommended that patients are then monitored at least quarterly for potential complications.	List price: £5500.00 per applicator. There is a patient access scheme in place for fluocinolone acetonide intravitreal implant.
Bevacizumab	Bevacizumab does not have a UK marketing authorisation for use in the eye.	Intravitreal injection Monitoring information not available as bevacizumab is not licensed for use in the eye.	Acquisition cost: £50.00 (lower limit reported in NICE DSU report)

3 Comments from consultees

3.1 The clinical experts agreed that, before anti-VEGF treatment, the standard of care for patients with diabetic macular oedema was laser photocoagulation therapy. One clinical expert highlighted that there are only a limited number of cases where laser photocoagulation has improved visual acuity rather than just reducing the progression of loss of vision. The patient group agreed that laser photocoagulation therapy is being used less now that pharmacological treatments are available and that anti-VEGFs have led to a significant change in the treatment of diabetic macular oedema (DMO).

3.2 The clinical experts stated that DMO that does not involve the centre of the macular is either observed (if visual acuity is not affected and thickening is greater than 500 µm from fovea) or treated with laser photocoagulation (if oedema or exudates are threatening the central fovea area). DMO involving the centre of the macular is treated with anti-VEGFs. Laser photocoagulation can have an adjunctive role and is still commonly used in the UK. Ranibizumab is used in people with CRT greater than 400µm (around 50% of patients). For people with CRT less than 400µm, therapies used include laser photocoagulation, observation until CRT becomes greater than 400µm, use of intravitreal bevacizumab (off licence) and intravitreal triamcinolone (off label). For people who have a pseudophakic lens whose disease has a sub-optimal response to anti VEGF treatment, intravitreal fluocinolone acetonide implant is used.

3.3 The patient group highlighted that diabetic macular oedema affects central vision and has a big impact on the day to day lives of patients, carers and their families. The condition does not affect peripheral vision and so the disease does not cause patients to go completely blind, however, patients expressed significant fear of losing their sight. The patient group stated that sight loss can lead to a forced early retirement; loss of income and dependence on benefits; loss of driving licence and independence; increased costs for visual aids, transport and domestic help; increased

risk of falls and accidents; dependence on family members; loss of confidence and self-esteem; social isolation; and clinical depression. They also stated that sight loss can affect patients' ability to self-manage their diabetes. The patient group stated that preventing deterioration of sight was the most important outcome for patients. The patient group stated that dexamethasone intravitreal implant would reduce the burden on patients because of the long-acting nature of the treatment.

3.4 The patient group stated that most patients felt dexamethasone intravitreal implant was beneficial and stopped their vision loss, however, some were unhappy with the side effects. Some patients did not want to use dexamethasone intravitreal implant again because of the increased risk of intraocular pressure, increased risk of developing glaucoma and increased risk of developing a cataract. The patient group reported that although patients were apprehensive about intravitreal injections, the thought of losing their sight made the procedure bearable. Some patients said that the dexamethasone intravitreal implant injection felt bigger than an anti-VEGF injection and caused a little more eye pain, however, many felt that the benefits of long acting treatment outweighed these disadvantages. The patient group stated that all patients prefer treatments with a low risk of complications and limited side effects.

3.5 The clinical experts agreed that dexamethasone intravitreal implant is already widely used for retinal vein occlusion and so there is expertise in place for its use in DMO. They agreed that dexamethasone intravitreal implant is a longer acting agent compared to ranibizumab, which may reduce the burden of injection and monitoring visits to the NHS.

3.6 Clinical experts and the patient group agreed that intravitreal dexamethasone intravitreal implant would be widely welcomed as an addition to the available treatments for DMO.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company identified 6 randomised controlled trials that compared dexamethasone intravitreal implant with a relevant comparator in adults with diabetic macular oedema (DMO). Of these, 3 were phase III studies (MEAD-010, MEAD-011, study 024) and 3 were phase II (PLACID, NCT00035906, and BEVORDEX). The MEAD studies, BEVORDEX and PLACID included patients with type 1 or type 2 diabetes; study 024 [redacted]; and NCT00035906 included people with diabetic and non-diabetic macular oedema. BEVORDEX included adults aged over 18 years; MEAD-010, MEAD-011, and PLACID only included adults aged 18 years or over; study 024 [redacted]; and NCT00035906 included people aged 12 years or older.

4.2 MEAD-010 and MEAD-011 were identical in design and provide the key data for dexamethasone intravitreal implant in the company submission. The studies compared dexamethasone 700 µg and dexamethasone 350 µg with sham in adults who had been previously treated 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 BCVA between 34 and 68 letters and a baseline CRT of 300 µm or more. Both studies lasted between 36 and 39 months. In both studies, patients received 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 1mm central macular subfield was

greater than 225 µm (until May 2010) or 175 µm (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 studies 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.

4.3 Study 024 was an open-label trial comparing dexamethasone 700 µg with ranibizumab 0.5 mg. It included adults with DMO involving the centre of the macular in at least 1 one eye. The study was 12 months long and took place at 57 study centres in 11 countries in Europe, Africa and North America. Patients were included if they had a baseline BCVA between 34 and 70 letters and a baseline CRT of 300 µm or more with a Spectralis device or 275 µm or more with a Cirrus device. Patients receiving dexamethasone intravitreal implant were treated at baseline, month 5 and month 10. Patients receiving ranibizumab were treated each month until there was stable vision for 3 consecutive months. Monthly ranibizumab injections were restarted if there was a decrease in vision and continued until stable vision was achieved again. The primary outcome was mean BCVA average change.

4.4 PLACID compared dexamethasone 700 µg in combination with laser photocoagulation with sham in combination with laser photocoagulation in 253 patients. Only adult patients with diffuse DMO (DMO with macular thickening involving the centre of the macular) were included. The study was 15 months long and took place at 48 centres in the US and Canada. Patients with a baseline BCVA between 34 and 70 letters and a CRT of at least 275 µm were included. Patients received either dexamethasone intravitreal implant or sham on the day of randomisation. At 1 month, all patients received laser photocoagulation treatment. Patients were evaluated for retreatment at 4, 6 and 9 months. Patients were eligible for retreatment if retinal thickness in the central macular subfield was 250 µm

or greater, if the following criteria were fulfilled: at least 3 months since the last laser photocoagulation treatment or 6 months since the last dexamethasone intravitreal implant, patient was not at significant risk from retreatment, and the patient would benefit from retreatment. Patients could receive up to 3 additional laser photocoagulation treatments (at months 4, 7 and 10) and 1 additional dexamethasone intravitreal implant or sham treatment (at month 6 or 9). The primary outcome was the proportion of patients who had at least a 10-letter improvement in BCVA from baseline at month 12.

4.5 NCT00035906 compared dexamethasone 700 µg and dexamethasone 350 µg with observation in 165 people in 29 retina practices in the US. The population included people with DMO or macular oedema associated with uveitis, retinal vein occlusion, or Irvine-Gass syndrome persisting at least 90 days after laser photocoagulation or medical treatment. The group of DMO patients in the study had macular oedema persisting for 90 days after laser photocoagulation or medical treatment and a BCVA between 35 and 67 letters. Patients received a single treatment at randomisation and were followed for 90 days. The primary outcome was the proportion of eyes achieving at least a 10 letter improvement in BCVA at day 90.

4.6 BEVORDEX compared dexamethasone 700 µg with bevacizumab 1.25 mg in adults with DMO affecting the fovea in at least 1 eye. 88 eyes were included. Patients were included if they had received prior laser photocoagulation therapy or if their condition was deemed unsuitable for laser photocoagulation therapy. Patients were included if they had a baseline BCVA between 17 and 72 letters and a baseline central retinal thickness of 300 µm or greater on spectral domain ocular tomography (or greater than 250 µm on time domain ocular tomography). The study took place at 7 study sites in Australia and lasted for 24 months. Patients who received dexamethasone intravitreal implant were treated at baseline and then were evaluated for retreatment every 6 weeks. Dexamethasone intravitreal implant was not given more often than every 4 months.

Patients who received bevacizumab received treatment at baseline, week 6 and week 12. From month 3 onwards, patients who received bevacizumab were evaluated for retreatment every 6 weeks (or every 4 weeks if persistent macular oedema was observed at 24 weeks). Retreatment criteria for both groups were CRT of 250 µm or greater on spectral domain or visual acuity less than 79 letters. The primary outcome was the proportion of eyes gaining 10 letters after 104 weeks.

4.7 The company did not present specific clinical data to address all of the comparators considered in the submission. The company stated that for people who have a pseudophakic lens, the relevant comparators are ranibizumab and laser photocoagulation. Study 024 used ranibizumab as a comparator and PLACID included laser photocoagulation as a comparator but neither study exclusively included people who had a pseudophakic lens. The company stated that relevant comparators for people who were unsuitable for or insufficiently responsive to non-corticosteroid therapy were fluocinolone acetonide implant and "watch and wait". MEAD-010, MEAD-011 and NCT00035906 used a proxy for watch and wait (sham treatment) as a comparator, but did not exclusively include people whose condition was unsuitable for or unresponsive to non-corticosteroid therapy. The company stated that the relevant comparator for people who had a pseudophakic lens and in whom ranibizumab and fluocinolone acetonide were not suitable was bevacizumab. BEVORDEX included bevacizumab as a comparator but did not exclusively include people who had a pseudophakic lens and whose condition was not suitable for ranibizumab or fluocinolone acetonide implants.

4.8 Health related quality of life and visual-functioning were assessed in the MEAD studies, PLACID [redacted] (see table 17 in the company's submission). In the MEAD studies, EQ-5D, NEI-VFQ 25 and SF-36 were assessed at baseline. SF-36 and EQ-5D were not assessed during follow up as they do not contain vision-specific items. 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.

4.9 The outcomes from the trials were analysed using an intention to treat approach. Missing data was accounted for by using a last observation carried forward approach. Subgroup analyses for patients with a pseudophakic lens and patients who had received prior treatment were presented in the company's submission.

4.10 The company identified 9 non-RCT studies that provided supportive evidence relevant to the populations included in the decision problem (CHAMPLAIN; Giralt et al., 2014; Mederios et al., 2014; MOZART; OCTOME; Pacella et al., 2013; Udaonda et al., 2013; and Zucchiatti et al., 2012). The company stated that there was a wide variety of results from the studies, from which no strong conclusions could be made. The company did not use the non-RCT data in its economic modelling. See section 6.2.7 of the company's submission for more information on the non-RCT studies.

ERG comments

Population

4.11 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.

4.12 The ERG stated that the treatment groups in the different trials were broadly comparable at baseline. The ERG believed that the baseline characteristics of the MEAD, PLACID and NCT00035906 trials were generally representative of the UK DMO population for whom treatment with dexamethasone would be considered.

Intervention and comparators

4.13 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, however 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.

4.14 The ERG highlighted that MEAD 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 µg). The ERG does not consider data from the trial arm using a lower dose of dexamethasone intravitreal implant to be relevant to the decision problem.

4.15 The ERG stated that the treatment algorithms used in the MEAD, PLACID and NCT00035906 trials were consistent with how dexamethasone would be used in clinical practice in the UK. However, the PLACID trial used laser photocoagulation concomitantly with dexamethasone, which the ERG did not consider to be in line with UK clinical practice.

4.16 The ERG noted that the company did not present data for fluocinolone acetonide implant in combination with laser photocoagulation or data for bevacizumab in combination with laser photocoagulation.

4.17 The ERG agreed with the company that observation and sham were appropriate surrogates for watch and wait.

Outcomes

4.18 The ERG stated that the Early Treatment Diabetic Retinopathy Study (ETDRS) method is a widely accepted method of assessing visual acuity in clinical trials.

4.19 The ERG stated that the safety parameters reported in the MEAD studies, PLACID and NCT00035906 were similar and included adverse events, intraocular pressure, biomicroscopic and ophthalmoscopic findings, and measures of diabetes control. The ERG considered these outcomes to be appropriate.

4.20 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.

Clinical trial results

4.21 In the MEAD studies presented by the company, the pooled results showed there was no statistically significant difference in the mean BCVA average change when dexamethasone intravitreal implant and sham were compared in the general diabetic macular oedema (DMO) population. Dexamethasone intravitreal implant resulted in a statistically significantly greater mean BCVA average change than sham in pseudophakic patients. See table 3 for the results of the MEAD studies.

Table 3. Primary clinical trial outcomes for dexamethasone intravitreal implant compared with sham (MEAD-010 and MEAD-011) [adapted from tables 20 to 23, pages 155 to 159 of company submission]

Study	Dexamethasone intravitreal implant	Sham	Dexamethasone intravitreal implant vs. sham p value
Mean BCVA average change (AUC approach; ETDRS letters, SD) – general DMO population			
MEAD-010	4.1 (8.3)	1.9 (7.7)	0.016
MEAD-011	2.9 (8.6)	2.0 (8.2)	0.366
MEAD Pooled	3.5 (8.4)	2.0 (8.0)	0.023
Mean BCVA average change (AUC approach; ETDRS letters, SD) – pseudophakic patients			
MEAD-010	8.1 (8.0)	2.1 (7.2)	<0.001
MEAD-011	4.9 (7.9)	1.3 (7.0)	0.018
MEAD Pooled	6.5 (8.1)	1.7 (7.1)	<0.001
BCVA improvement of 15 letters or more (n, %) – general DMO population			
MEAD-010	36 (22.1)	22 (13.3)	0.038
MEAD-011	42 (22.3)	20 (10.8)	0.003
MEAD Pooled	78 (22.2)	42 (12.0)	<0.001
BCVA improvement of 10 letters or more (n, %) – general DMO population			
MEAD-010	63 (38.7)	38 (23.0)	0.002
MEAD-011	65 (34.6)	46 (24.9)	0.040
MEAD Pooled	128 (36.5)	84 (24.0)	<0.001
Abbreviations: AUC, area under the curve; BCVA, best corrected visual acuity; EDTRS, Early Treatment of Diabetic Retinopathy Study; NEI-VFQ-25, National Eye Institute-Visual Functioning Questionnaire; SD, standard deviation.			

4.22 In Study 024, ranibizumab resulted in a [redacted] compared with dexamethasone intravitreal implant (see table 4).

Table 4. Primary clinical trial outcomes for dexamethasone intravitreal implant compared with ranibizumab (Study 024) [adapted from tables 27 and 28 on pages 170 and 172 of company's submission]

Outcome	Dexamethasone intravitreal implant	Ranibizumab	P-value
BCVA			
Mean average change (ETDRS letters, SD)	[redacted]	[redacted]	[redacted]
Mean average change, AUC approach (ETDRS letters, SD)	[redacted]	[redacted]	[redacted]
Improvement of 15 letters or more (n, %)	[redacted]	[redacted]	NR
Loss of 15 letters or more (n, %)	[redacted]	[redacted]	NR
Abbreviations: AUC, area under the curve; BCVA, best corrected visual acuity; EDTRS, Early Treatment of Diabetic Retinopathy Study			

4.23 In PLACID, dexamethasone intravitreal implant plus laser resulted in statistically significantly more eyes with a BCVA improvement of 10 letters or more compared with laser alone after 1 month. However, the difference between the two groups was not statistically significant at months 4, 6, 7, 9 or 12 (see table 5).

Table 5. Clinical trial outcomes for dexamethasone intravitreal implant plus laser compared with laser alone (PLACID) [adapted from table 31 on page 176 of company's submission]

Outcome	**Dexamethasone** intravitreal implant **+ laser**	Laser alone	P-value
BCVA improvement of 10 ETDRS letters or more (n, %)			
Month 1	40 (31.7)	14 (11.0)	<0.001
Month 4	33 (26.2)	21 (16.5)	0.060
Month 6	28 (22.2)	22 (17.3)	0.326
Month 7 (1 month post retreatment)	28 (38.4)	14 (19.4)	0.014
Month 9	40 (31.7)	22 (17.3)	0.007
Month 12	35 (27.8)	30 (23.6)	0.453
Abbreviations: BCVA, best corrected visual acuity; EDTRS, Early Treatment of Diabetic Retinopathy Study			

4.24 In NCT00035906, statistically significantly more patients achieved a 10 or more letter improvement or a 15 or more letter improvement in visual acuity with dexamethasone intravitreal implant compared with observation

at days 60 and 90, however, there was no significant difference between the treatment groups for either outcome at day 180.

4.25 In BEVORDEX, there was no statistically significant difference between dexamethasone intravitreal implant and bevacizumab for the improvement in BCVA of 10 letters or more in the general DMO population or in mean change in BCVA in the pseudophakic population (see table 6).

Table 6. Clinical trial outcomes for dexamethasone intravitreal implant compared with bevacizumab (BEVORDEX) [adapted from text on page 181 of company's submission]

Outcome	Dexamethasone intravitreal implant	Bevacizumab	P-value
BCVA – all patients			
Improvement of 10 letters or ETDRS more (n, %)	19 (41%)	17 (40%)	0.99
Loss of 10 letters or ETDRS more (n, %)	5 (11%)	0	Not reported
Mean improvement	5.6 (95% CI 0.90 to 10.4)	8.9 (6.27 to 11.6)	0.24
BCVA – pseudophakic patients			
Mean change	10.4	7.7	0.47
Abbreviations: BCVA, best corrected visual acuity; EDTRS, Early Treatment of Diabetic Retinopathy Study			

4.26 There were no statistically significant differences in the average change in health related quality of life when comparing dexamethasone intravitreal implant with sham in the MEAD studies. The company argued that the health related quality of life of patients receiving dexamethasone intravitreal implant was being negatively affected by lens opacification and primary cataract formation. A post-hoc analysis performed by the company showed that after cataract surgery the improvement in vision-related quality of life associated with dexamethasone use was greater than that before cataract formation and it was similar to the improvement reported in pseudophakic patients. See tables 7 and 8 for health related quality of life data reported from the MEAD studies. See tables 29 and 30 and page 179 of the company's submission for health related quality of life data reported in study 024 and PLACID.

Table 7. Distribution of EQ-5D scores at baseline in MEAD studies (pooled across both dexamethasone arms and sham) [table 93 on page 374 of company's submission]

	Patients treated in better seeing eye						
	Overall	**Health State 1**	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Patients treated in worse seeing eye						
	Overall	**Health State 1**	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: NA, not applicable							

Table 8. NEI-VFQ-25 data reported in the MEAD studies [adapted from table 26 on page 167 and figure 22 on page 168 of company's submission]

	Dexamethasone intravitreal implant	Sham	P value
Mean average change from baseline in NEI-VFQ-25 (AUC approach)			
Overall composite score	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]
Difficulty with near vision	[redacted]	[redacted]	[redacted]
Difficulty with distance vision	[redacted]	[redacted]	[redacted]
Meant health symptoms due to vision	[redacted]	[redacted]	[redacted]
Mean VFQ-25 average change from baseline in near-vision subscale			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AUC, area under the curve; NR, not reported			

4.27 The mean number of dexamethasone intravitreal implant treatments per patient in the MEAD trials was 4.1. Fewer than 10% of patients received therapy every 6 months. In PLACID, 73 (57.9%) of the patients receiving dexamethasone intravitreal implant plus laser received retreatment with dexamethasone intravitreal implant at month 6 and 9 (7.1%) received retreatment at month 9.

4.28 In the MEAD studies, 36% of patients in the dexamethasone group 700 µg group and 57% of patients in the sham treatment group discontinued from the study. In PLACID, 16 (13%) patients in the dexamethasone intravitreal implant plus laser group and 27 (21%) patients in the laser monotherapy group discontinued treatment. In NCT0035906, 7 (12%) patients in the dexamethasone 700 µg group discontinued treatment and 8 (14%) patients in the observation group discontinued from the study.

4.29 There were 9 deaths in the dexamethasone intravitreal implant group and 5 deaths in the sham group in the MEAD studies. None of these deaths

were related to treatment. There were 2 deaths in the group of DMO patients receiving dexamethasone intravitreal implant in NCT00035906, although it is not clear whether these were treatment related deaths, and there were no deaths in the sham arm. In the PLACID study 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. In study 024 there was 1 death in the dexamethasone intravitreal implant group and 3 deaths in the ranibizumab group. It was not reported whether these were treatment related.

Adverse effects of treatment

4.30 The most common ocular treatment-related adverse events in the MEAD studies were cataract formation and raised intra-ocular pressure with dexamethasone intravitreal implant and conjunctival haemorrhage with sham. In the MEAD studies, treatment related adverse events were reported in 244 (70.3%) of the dexamethasone intravitreal implant treated eyes and 90 (25.7%) of the eyes that received sham treatment. These were serious in 115 (33.1%) and 83 (23.7%) of eyes respectively. Amongst patients with a pseudophakic lens, serious treatment related adverse events were reported in 2 (2.4%) of the dexamethasone intravitreal implant treated eyes and none of the eyes that receive sham treatment. Treatment was discontinued because of adverse events in 45 (13.0%) of patients receiving dexamethasone intravitreal implant and 40 (11.4%) of patients receiving sham in the MEAD studies.

4.31 In study 024, [redacted] of the dexamethasone intravitreal implant treated eyes and [redacted] of the ranibizumab treated eyes had treatment related adverse events. These were serious in [redacted] and [redacted] of the eyes respectively. The number of treatment related adverse events in patients with a pseudophakic lens was not reported in the company's submission.

4.32 In PLACID, treatment related adverse events were reported in 52 (41.6%) of eyes treated with dexamethasone intravitreal implant plus laser and in 24 (18.9%) of the eyes treated with laser 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.

4.33 The number of treatment related adverse events was not reported for BEVORDEX or NCT0035906. There were no serious treatment related adverse events in the dexamethasone intravitreal implant group in NCT0035906.

Subgroup analyses

People with a pseudophakic lens

4.34 The mean BCVA change from baseline for the patients with a pseudophakic lens in the MEAD studies was statistically significantly greater with dexamethasone compared with sham.

4.35 There were fewer ocular AEs in the study eye in patients with a pseudophakic lens at baseline who were randomised to dexamethasone compared with in the whole diabetic macular oedema (DMO) population. This is a result of the absence of the primary cataract adverse events seen in the patients without a pseudophakic lens treated with dexamethasone in the whole DMO population. In PLACID, there were fewer adverse events, ocular adverse events and ocular treatment-related adverse events in the people with a pseudophakic lens compared to the whole DMO population.

People who had received prior treatment

4.36 In the subgroups reported in the MEAD studies based on prior treatments received, dexamethasone generally resulted in a greater reduction in CRT and greater improvement in BCVA compared with sham. Safety and adverse events data for people who had received prior therapy showed a similar safety profile for dexamethasone to the whole DMO population.

4.37 In the MEAD studies, dexamethasone resulted in a statistically significantly greater improvement in mean BCVA average change

compared with sham in several of the subgroup analyses (diabetes duration 15 years or less, diabetic macular oedema duration 1.5 years or less, patients with HbA1c of 8% or less, and patients with severe non-proliferative diabetic retinopathy or worse at baseline).

ERG comments

Treatment effectiveness results

4.38 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, people who are considered insufficiently responsive to, and people who are unsuitable for non-corticosteroid therapy). 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.

4.39 The ERG highlighted that the data presented by the company in relation to the impact of cataract on health-related quality of life was from a post hoc analysis and was for near-vision rather than for the overall composite NEI-VFQ-25 score, therefore it should be interpreted with caution.

4.40 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.

Treatment discontinuation

4.41 The ERG stated that the results of the MEAD studies are potentially flawed because of high discontinuation rates across the trial arms (36% in the dexamethasone 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 studies. 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 studies were higher than discontinuation rates seen with dexamethasone intravitreal implant in the other RCTs.

Subgroup analyses

4.42 The ERG acknowledged that people with a pseudophakic lens in the dexamethasone intravitreal implant group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population (6.5 letters in the pseudophakic subgroup compared with 3.5 in the whole trial ITT population). However, the ERG's clinical experts suggested that a difference of 3 letters between treatment groups may therefore not represent a clinically meaningful change in BCVA to the patient, and a change of 5 letters or more is likely to represent a clinically significant change.

Network meta-analyses

4.43 As there were no head to head trials comparing dexamethasone with all of the relevant comparators, the company carried out a network meta-analysis. The network meta-analysis included the 6 trials already identified, plus 6 other randomised controlled trials identified in a systematic review carried out specifically for the network meta-analysis (BOLT, ETDRS, Olk [1986], PROTOCOL 1, RESTORE, and REVEAL). The network meta-analysis included 2 trials that compared dexamethasone intravitreal implant with sham or no treatment (MEAD-010 and MEAD-011). It also 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 (BOLT), dexamethasone intravitreal implant plus laser compared with laser alone (PLACID), and dexamethasone intravitreal implant compared with bevacizumab (BEVORDEX).

4.44 A summary of the trials included in the network meta-analysis is presented in table 9.

Table 9. Summary of the trials included in the network meta-analysis [table 35 on page 192 of company's submission]

No. of trials	Trial Reference	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3
1	024	Dexamethasone	Ranibizumab	-
1	BOLT	Bevacizumab	Laser photocoagulation	-
1	PLACID	Dexamethasone + laser photocoagulation	Laser photocoagulation	-
1	BEVORDEX	Dexamethasone	Bevacizumab	-
2	ETDRS (Hornberger) Olk	Laser photocoagulation	Sham/No treatment	-
2	MEAD-010 MEAD-011	Dexamethasone	Sham/No treatment	-
3	PROTOCOL I RESTORE REVEAL	Ranibizumab + laser photocoagulation	Ranibizumab	Laser photocoagulation

4.45 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, change of less than 10 letters and 10 letter gain for the general DMO population of the study and for the subgroup of patients who had a pseudophakic lens. The BCVA data from each of the trials was split into the following three categories: worsening, defined as loss of 10 or more letters at 12 months; stable, defined as loss or gain of <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. A subgroup analysis was conducted to assess the impact of people having a pseudophakic lens at baseline on the efficacy outcomes

4.46 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.

4.47 The incidence of cataracts, raised intraocular pressure, retinal detachment, endophthalmitis and vitreous haemorrhage in the trials included in the network meta-analysis are presented in table 10.

Table 10. Incidence of cataract, raised intraocular pressure, retinal detachment, endophthalmitis and vitreous haemorrhage in the trials included in the network meta-analysis [adapted from table 70 on page 214 of the ERG report]

	Year	Dexa	Rani	Beva	Laser	Flu ace
Relevant trial	-	MEAD	RESTORE	BOLT	PROTOCOL 1	FAME
Cataract requiring extraction in patients without a pseudophakic lens	1	8.4% (11.8%)	NA	NA	NA	0.00%
	2	19.2% (37.7%)	NA	NA	NA	65.5%
	3	2.9% (26.4%)	NA	NA	NA	42.0%
Raised IOP treated with medication or surgery	1	12.1%	0.9%	9.5%	[redacted]	0.0%
	2	4.6%	0.0%	0.0%	[redacted]	4.8%
	3	1.2%	0.0%	0.0%	[redacted]	32.3%
Retinal detachment	1	0.0%	0.0%	0.0%	0.0%	0.0%
	2	0.3%	0.0%	0.0%	[redacted]	0.0%
	3	0.3%	0.0%	0.0%	[redacted]	0.0%
Endophthalmitis	1	0.3%	0.0%	0.0%	[redacted]	0.0%
	2	0.3%	0.0%	0.0%	[redacted]	0.0%
	3	0.0%	0.0%	0.0%	[redacted]	0.0%
Vitreous haemorrhage	1	4.0%	0.0%	0.0%	[redacted]	0.0%
	2	1.2%	0.0%	0.0%	[redacted]	0.0%
	3	1.7%	0.0%	0.0%	[redacted]	0.0%

Abbreviations: Beva, bevacizumab; Dexa, dexamethasone intravitreal implant; Flu ace, fluocinolone acetonide; IOP, intraocular pressure; NA, not applicable; Rani, ranibizumab
Note: ERG corrected proportions for cataract requiring extraction in patients without a pseudophakic lens for dexamethasone intravitreal implant (all years), raised IOP for laser (Year 1) and vitreous haemorrhage for laser (Year 3) are presented in brackets following clarification from the company; with the exception of cataract proportions, all other figures reported in this table are those that have been used in the original economic models submitted by the company. Cataract surgery is not applicable to pseudophakic patients, hence not applicable to ranibizumab, bevacizumab or laser therapy.

4.48 The company also conducted a subgroup analysis to assess the impact of people having a pseudophakic lens at baseline on the efficacy outcomes. The network included the same trials and pathways as the network for the general DMO population, but used data on people with a pseudophakic lens where available. For trials where data on people with a pseudophakic lens were not reported separately (Olk [1986], ETDRS, BOLT, BEVORDEX, REVEAL or RESTORE), the company used general DMO population data. The results of the network meta-analysis for the subgroup of people with a pseudophakic lens were similar to those for the general DMO population, however, dexamethasone intravitreal implant

plus laser was not associated with a statistically significantly higher risk of gaining or losing at least 10 letters compared with sham or no treatment.

4.49 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.

4.50 Sensitivity analyses were conducted for the network meta-analysis based on data from the FAME trial, which compared fluocinolone acetonide with sham. The company reported that the results for the 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.

4.51 The company also 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 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 pair wise meta-analysis of losing 10 or more letters was 0.72 (95% CrI [0.35, 1.25]) which is different to the relative risk from the network meta-analysis of 0.71 (95% CrI [0.41, 1.08]). The relative risk for gaining at least 10 letters at 12 months from the pair wise meta-analysis is 1.35 (95% CrI [0.77, 2.21]) which differs from the relative risk from the network meta-analysis of 1.40 (95% CrI [0.92, 2.14]).

ERG comments

4.52 The ERG highlighted that the methodology 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 the following reasons:

- The results of the network meta-analysis and the pairwise meta-analyses from the MEAD trials for dexamethasone intravitreal implant compared with sham or no treatment provided different results. The results should be very similar as only the MEAD trials informed the comparison of dexamethasone intravitreal implant with sham/no treatment in the network meta-analysis. The company did not provide details of the data used in the pair wise meta-analysis and so the ERG was unable to validate the results of the analyses. Furthermore, the ERG commented in the erratum to the ERG report that the corrected figures for the NMA and pairwise meta-analysis do not change the ERG's view on the validity of the NMA.
- There were high levels of clinical and statistical heterogeneity in the network meta-analyses, which was 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 NMAs and the sensitivity analyses were quite wide and thus there is a large amount of uncertainty around the efficacy estimates.
- The dexamethasone dosing regimens used in the ranibizumab and bevacizumab trials, the comparability of the trials linking dexamethasone with the other treatments in the network, and the poor fit of the models to the datasets (as indicated by the between study standard deviation). The ERG thus considered that the results reported from the NMAs should be interpreted with caution.

5 Cost-effectiveness evidence

Model structure

5.1 The company submitted an economic evaluation that, in the base case, compared dexamethasone intravitreal implant with watch and wait for patients with diabetic macular oedema (DMO) who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy, and compared dexamethasone with ranibizumab for people with DMO

who have a pseudophakic lens. The company carried out additional analyses comparing dexamethasone intravitreal implant with fluocinolone acetonide implant in people whose disease is insufficiently responsive to non-corticosteroids and laser photocoagulation, and with bevacizumab and watch and wait in people with a pseudophakic lens. 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. The model had 3-monthly cycles and a time horizon of 15 years.

5.2 For patients with DMO who are considered unsuitable for non-corticosteroid therapy, dexamethasone intravitreal implant was considered as a first or second line treatment option. For patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy, dexamethasone intravitreal implant was considered second line treatment after non-corticosteroid therapy (such as ranibizumab, bevacizumab and laser). The company considered the most appropriate comparator for both populations was watch and wait. 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 the general DMO population and this group.

5.3 For patients with visual impairment due to 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 was ranibizumab, as this is the most common first-line treatment for DMO. The analysis was based on the network meta-analysis for people with a pseudophakic lens. This included data from the subgroup of patients with a pseudophakic lens in the pooled MEAD clinical studies and data for the subgroups of people with a pseudophakic lens in the other trials in the network where available. If data from people with a pseudophakic lens were not available in the trials, data for the whole DMO population were used instead in order to enable the network to be constructed.

5.4 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 (see table 11 for baseline distributions of visual acuity). Patients entering the model may be affected by DMO in either their BSE or WSE (unilateral DMO), or both eyes (bilateral DMO), with the proportions determined by the number of patients in these groups in the dexamethasone intravitreal implant treatment arm of the pooled MEAD. The proportions are assumed to vary by population.

Table 11. Company's baseline distribution of vision across visual acuity states [adapted from tables 71 and 72 on pages 335 and 336 of company's submission]

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
General DMO population							
Unilateral DMO in the BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pseudophakic population							
Unilateral DMO in the BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.							

ERG comments on model structure

5.5 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 comparison and populations submitted were appropriate to inform the decision problem.

Model details

5.6 Both eyes could transition independently between 6 visual acuity states. The health states were defined by a 10 letter range in BCVA as shown in table 12. 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. Half cycle correction and a discount rate of 3.5% for QALYs and costs were applied. An NHS/PSS perspective was used.

Table 12. Company's model – health state definition [table 61 on page 312 of company's submission]

	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
ETDRS letters	≤35	36–45	46–55	56–65	66–75	≥76
Approximate Snellen equivalents at 6m/20ft	≤6/60	6/60–6/38	6/38–6/24	6/24–6/15	6/15–6/10	≥6/10
	≤20/200	20/200 to 20/125	20/125 to 20/80	20/80 to 20/50	20/50 to 20/32	≥20/32
Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study.						

5.7 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 only occur at the end of year 1 or year 2. Patients with bilateral DMO were assumed to receive the same treatment in both eyes. Patients could discontinue treatment because of adverse events or loss of efficacy of treatment.

5.8 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 due to diabetes and due to DMO. The model assumed that mortality occurred equally across all visual acuity states. There was no additional mortality due to blindness in the base case (although this was tested in sensitivity analyses).

5.9 The model assumed a maximum treatment duration of 3 years. The average number of treatments per year used in the model was taken from the clinical trials. The model allowed the use of rescue therapy with laser for some interventions, although not in the comparison of dexamethasone with watch and wait.

5.10 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 studies. For relative effects, the transition probabilities for watch and wait and ranibizumab (and bevacizumab, laser, and fluocinolone acetonide in the sensitivity and scenario analyses) were calculated by applying the relative risks from the network meta-analysis to the 3-month transition probabilities for dexamethasone (baseline treatment). If treatment was discontinued, visual acuity was assumed to follow the natural history of vision in eyes with DMO. Eyes without DMO are assumed to maintain constant vision.

5.11 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 pseudophakic population, except there was no risk of cataract in the pseudophakic population. Adverse effects did not have any effect on health related quality of life in the model.

5.12 The company concluded that the published utility values used within TA274 and TA301 were subject to a large number of limitations: Firstly the published utility values corresponded to visual impairment resulting from causes other than DMO, secondly the majority of utility values were based on vision in the BSE only, requiring assumptions for the impact of vision resulting from treatment of the WSE or bilateral treatment; thirdly the health states for which utility values were available did not match the

health states in the company's model, thus requiring adjustments or assumptions to make the published utility data 'fit' within model structures.

5.13 Health related quality of life in the model was dependent on the patient's visual acuity. The company conducted their analyses using the Visual Function Questionnaire utility index (VFQ-UI) data obtained from the MEAD clinical trials which 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-25 data was 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.

5.14 The utility values associated with the different visual acuity states are presented in tables 13 and 14.

Table 13. Utility values for visual acuity states (all diabetic macular oedema patients) [table 100 on page 390 of company's submission]

		Better seeing eye					
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Worse seeing eye	Health State 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 2	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 3	-	-	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 4	-	-	-	[redacted]	[redacted]	[redacted]
	Health State 5	-	-	-	-	[redacted]	[redacted]
	Health State 6	-	-	-	-	-	[redacted]

Table 14. Utility values for visual acuity states (people with a pseudophakic lens) [table 101 on page 390 of company's submission]

		Better seeing eye					
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Worse seeing eye	Health State 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 2	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 3	-	-	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 4	-	-	-	[redacted]	[redacted]	[redacted]
	Health State 5	-	-	-	-	[redacted]	[redacted]
	Health State 6	-	-	-	-	-	[redacted]

5.15 The company used NHS reference costs and the Monthly Index of Medical Specialities to cost resources associated with the treatment of DMO including: intervention costs, monitoring and test costs, health state costs, adverse event costs. The different treatments were costed as follows: dexamethasone intravitreal implant £870.00, ranibizumab £742.17, and fluocinolone acetonide £5500. Laser photocoagulation was assumed to have zero cost as all facilities 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 DSU report on the use of bevacizumab in eye conditions. Ranibizumab and fluocinolone acetonide both have a patient access scheme (PAS) and scenario analyses varying the discount to the list price were provided by the company. The cost of administration of laser was assumed to be £116.68. All intravitreal injections were assumed to be performed in the outpatient setting at a cost of £116.68. For the sensitivity analyses where a day case procedure is assumed, the cost is £356.35. The assumed total costs per round of treatment are presented in table 15.

Table 15. Total cost per round of treatment [adapted from table 104 on page 404 of company's submission]

Treatment	Total cost per round of treatment	
	Unilateral DMO	Bilateral DMO
Dexamethasone intravitreal implant	£986.68	£1944.19
Ranibizumab	£858.85	£1659.36
Bevacizumab	£166.68	£275.02
Laser	£116.68	£116.68
Fluocinolone Acetonide	£5616.68	£11,204.19
Abbreviations: DMO, diabetic macular oedema.		

5.16 The costs of monitoring and tests were as follows, all sourced from NHS reference costs: routine monitoring visit £80.04, optical coherence tomography £18.06, fluorescein angiography £116.68, and intraocular pressure check £80.04. The costs of monitoring and treatment are assumed 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).

5.17 The number of monitoring visits required for each treatment in the model is outlined in table 16.

Table 16. Treatment and monitoring visits required for each treatment used in the company's model [adapted from tables 106 to 112 on pages 406 to 408 of company's submission and table 55 on page 183 of ERG report]

Treatment		Number of treatments			Source
		Year 1	Year 2	Year 3+	
All patients with diabetic macular oedema					
Watch and wait	Treatment	0	0	0	-
	Monitoring	4	4	4	TA271 (Fluocinolone acetonide).
Dexa	Treatment	[redacted]	[redacted]	[redacted]	MEAD data.
	Monitoring	4	4	4	SmPC and clinical opinion.
Flu ace	Treatment	1.00	0.26	0.26	FAME study.
	Monitoring	4	4	4	TA271 (fluocinolone acetonide).
Patients with diabetic macular oedema who have a pseudophakic lens					
Dexa	Treatment	[redacted]	[redacted]	[redacted]	MEAD data.
	Monitoring	4	4	4	SmPC and clinical opinion.
Rani	Treatment	7.00	3.90	2.90	RESTORE study (data from all DMO patients)
	Monitoring	12	10	4	TA237 (ranibizumab).
Beva	Treatment	9.00	4.00	2.90	BOLT study to year 2 then assumed equal to ranibizumab (data from all DMO patients).
	Monitoring	12	10	4	Assumed equal to ranibizumab.
Laser	Treatment	[redacted]	[redacted]	[redacted]	PROTOCOL I to year 2, then LOCF.
	Monitoring	4	4	4	TA271 (fluocinolone acetonide).
Watch and wait	Treatment	0	0	0	-
	Monitoring	4	4	4	TA271 (fluocinolone acetonide).
Abbreviations: Beva, bevacizumab; Dexa, dexamethasone intravitreal implant; Flu ace, fluocinolone acetonide; Laser, laser photocoagulation; LOCF, last observation carried forward; Rani, ranibizumab.					

5.18 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 raised IOP per patient was £262.40 for medical management and £1222.93 for surgical management (as per the company model, the total average cost of raised IOP per patient was reported incorrectly in the company submission). 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.

ERG comments

Health-related quality of life

5.19 Modelling transitions in BCVA states independently for each eye was an improvement over previous economic models assessing treatment for DMO as it allowed a more realistic representation of patient experience and a more accurate estimate of health related quality of life as it considered the impact of each of the BSE and WSE on HRQOL separately.

5.20 The use of the VFQ-UI is more relevant to people with diabetic macular oedema (DMO) than the EQ-5D because it contains vision-specific items. In addition, the EQ-5D is relatively insensitive to changes in visual functioning.

Modelling assumptions and approach

5.21 The ERG stated that the economic analysis adopted a number of assumptions and approaches which 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 economic model assumed 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. However the evidence from the MEAD trials suggests that this assumption is not correct.
- The ‘normalisation’ 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.

5.22 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 (see section 5.37) showed that this restriction did not reflect trial evidence.

5.23 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 those who are insufficiently responsive to non-corticosteroid therapy. The ERG were aware, however, that the data analysis that would be needed to include fluocinolone acetonide intravitreal implant in the base case had considerable limitations.

5.24 The ERG argued that laser photocoagulation should have been included in the base case analysis of patients who have a pseudophakic lens as it is routine clinical practice in patients with diabetic macular oedema (DMO) and CRT less than 400 microns.

Costs

5.25 Costs were appropriately captured in the company's submission overall. However, the ERG noted that the company may have overestimated the cost associated with severe vision loss (i.e. BCVA < 35 letters) because of an overestimation of the cost of residential care which was one of its components. The company used the unit cost of residential care provided by local authority, however previous economic analyses in TAs have used the unit cost of private residential care, with views expressed that the private sector appears to be 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 local authority. If private sector is the main provider of residential care, then use of the unit cost of local

authority residential care by the company has seriously overestimated the cost associated with severe vision loss.

Company's base-case results

5.26 In the company's base case, dexamethasone intravitreal implant dominated watch and wait for patients who are considered unsuitable for non-corticosteroid therapy and patients who are considered insufficiently responsive to non-corticosteroid therapy. In the pseudophakic population, treatment with ranibizumab resulted in an ICER of £50,905 per QALY gained compared with dexamethasone intravitreal implant when the list price of ranibizumab was used. When a discount of 50% was applied to the list price of ranibizumab, ranibizumab dominated dexamethasone intravitreal implant. The base case results are presented in tables 17 and 18.

Table 17. Company's base case results; patients who are considered unsuitable for non-corticosteroid therapy and patients who are considered insufficiently responsive to non-corticosteroid therapy [adapted from tables 129 and 130 on page 438 of company's submission]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (per QALY gained)
Deterministic results					
Dexamethasone	£20,413	5.7420	-	-	-
Watch and wait	£21,882	5.6764	£1469	-0.0656	Dexamethasone dominates
Probabilistic results					
Dexamethasone	£20,827	5.7789			
Watch and wait	£22,536	5.7230	£1708	-0.0559	Dexamethasone dominates
Abbreviations: Dexamethasone, dexamethasone intravitreal implant; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Table 18. Company's base case results; patients who have a pseudophakic lens [adapted from tables 133 and 134 on page 440 of company's submission]

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (per QALY gained)
Deterministic results					
Dexamethasone	£15,720	5.0886	-	-	-
Ranibizumab	£21,724	5.2066	£6004	0.1179	£50,905
Probabilistic results					
Dexamethasone	£16,053	5.1422	-	-	-
Ranibizumab	£22,762	5.2172	£6710	0.0749	£89,531
Deterministic results (50% discount in list price of ranibizumab)					
Dexamethasone	£15,720	5.0886	-	-	-
Ranibizumab	£15,004	5.2066	-£716	0.1179	Ranibizumab dominates
Probabilistic results (50% discount in list price of ranibizumab)					
Dexamethasone	£16,053	5.1422	-	-	-
Ranibizumab	£16,037	5.2172	-£15	0.0749	Ranibizumab dominates
Abbreviations: Dexamethasone, dexamethasone intravitreal implant; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALYs, quality-adjusted life years.					

5.27 The main driver of the base-case cost effectiveness results for patients who are considered unsuitable for non-corticosteroid therapy and patients who are considered insufficiently responsive to non-corticosteroid therapy was the cost of residential care. The main driver for people who have a pseudophakic lens was the relative risk of worsening vision obtained from the network meta-analysis.

Company sensitivity analyses and scenarios

5.28 The company carried out one-way sensitivity analyses and scenario analyses to assess the impact on the deterministic results. In the company's sensitivity analyses, dexamethasone intravitreal implant remained cost-effective compared with watch and wait in patients who are considered unsuitable for non-corticosteroid therapy and for patients who are considered insufficiently responsive to corticosteroid therapy. The ICERs were most sensitive to changes to the cost of residential care and the percentage of patients requiring residential care. Dexamethasone

intravitreal implant remained cost-effective compared with ranibizumab at list price for patients who have a pseudophakic lens. The ICERs were most sensitive to changes to the relative risk of worsening vision and the proportion of outpatient procedures for ranibizumab.

5.29 The company performed 28 scenario analyses. The scenarios that had a significant impact on the ICER are reported here. Details of all of the scenario analyses can be found in section 7.6.1 of the company's submission.

5.30 For patients who were unsuitable for non-corticosteroid therapy and patients who were considered insufficiently responsive to non-corticosteroid therapy, dexamethasone intravitreal implant continued to dominate in the majority of the scenarios. For patients who were insufficiently responsive to non-corticosteroid therapy, fluocinolone acetonide intravitreal implant dominated dexamethasone intravitreal implant and watch and wait when a discount of 20% or more was applied to the list price of fluocinolone acetonide. The scenario analyses for these 2 populations where dexamethasone intravitreal implant did not dominate watch and wait are shown in table 19. The results for the sensitivity analyses for fluocinolone acetonide intravitreal implant at list price and discounts of 10% and 20% are shown in table 20.

Table 19. Scenario analyses for patients who were unsuitable for non-corticosteroid therapy or who were considered insufficiently responsive to non-corticosteroid therapy where dexamethasone intravitreal implant did not dominate [adapted from tables 143, 144, 145 and 148 on pages 460 to 462 of company's submission]

Scenario	Treatment	Total costs	Total QALYs	Inc. cost	Inc. QALY	ICER (per QALY gained)
1 year time horizon	Watch and wait	£711	0.6012	-	-	-
	Dexamethasone	£3435	0.6027	£2724	0.0015	£1,822,946
5 year time horizon	Watch and wait	£7214	2.6290	-	-	-
	Dexamethasone	£10,785	2.6571	£3571	0.0281	£127,034
10 year time horizon	Watch and wait	£15,649	4.4869	-	-	-
	Dexamethasone	£15,985	4.5398	£337	0.0529	£6365
100% unilateral DMO in WSE (no fellow eye involvement)	Watch and wait	£5104	5.7964	-	-	-
	Dexamethasone	£9468	5.8297	£4364	0.0332	£131,276

Abbreviations: Dexamethasone, dexamethasone intravitreal implant; Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio; WSE, worse seeing eye.

Table 20. Scenario analysis 1 results for patients who were considered insufficiently responsive to non-corticosteroid therapy [adapted from tables 163 to 165 on page 467 of company's submission]

Technologies	Total		Incremental		ICER (cost per QALY gained)	ICER vs. baseline (dex)
	Costs	QALYs	Costs	QALYs		
List price for fluocinolone acetonide						
Dexamethasone	£20,413	5.7420	-	-	-	-
Watch and wait	£21,877	5.6765	£1464	-0.0655	Dex dominates	Dex dominates
Flu ace	£22,365	5.8214	£1953	0.0794	£24,591*	£24,591
10% discount price for fluocinolone acetonide						
Dexamethasone	£20,413	5.7420	-	-	-	-
Flu ace	£21,226	5.8214	£813	0.0794	£10,241	£10,241
Watch and wait	£21,877	5.6765	£651	-0.1449	FA dominates	Dex dominates
20% discount price for fluocinolone acetonide						
Flu ace	£20,086	5.8214	-	-	-	-
Dexamethasone	£20,413	5.7420	£326	-0.0794	FA dominates	FA dominates
Watch and wait	£21,877	5.6765	£1790	-0.1449	FA dominates	FA dominates

Abbreviations: Dex/Dexamethasone, dexamethasone intravitreal implant; FA/Flu ace, fluocinolone acetonide; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

* Versus dexamethasone intravitreal implant.

5.31 The results for scenario 1 for people with a pseudophakic lens are shown in table 21. A discount of 50% to the list price of ranibizumab was used for the other analyses. In most of the other scenario analyses, ranibizumab dominated dexamethasone intravitreal implant. The results of the scenario analyses where ranibizumab did not dominate dexamethasone intravitreal implant are presented in table 22.

Table 21. Scenario analysis 1 results for patients with a pseudophakic lens [adapted from tables 195 to 200 on pages 477 and 478 of company's submission]

Treatment	Total		Incremental		ICER (cost per QALY)
	Costs	QALYs	Costs	QALYs	
List price for ranibizumab					
Dexamethasone	£15,720	5.0886	-	-	-
Ranibizumab	£21,724	5.2066	£6004	0.1179	£50,905
10% discount price for ranibizumab					
Dexamethasone	£15,720	5.0886	-	-	-
Ranibizumab	£20,380	5.2066	£4660	0.1179	£39,510
20% discount price for ranibizumab					
Dexamethasone	£15,720	5.0886	-	-	-
Ranibizumab	£19,036	5.2066	£3316	0.1179	£28,116
30% discount price for ranibizumab					
Dexamethasone	£15,720	5.0886	-	-	-
Ranibizumab	£17,692	5.2066	£1972	0.1179	£16,721
40% discount price for ranibizumab					
Dexamethasone	£15,720	5.0886	-	-	-
Ranibizumab	£16,348	5.2066	£628	0.1179	£5327
50% discount price for ranibizumab					
Ranibizumab	£15,004	5.2066	-	-	-
Dexamethasone	£15,720	5.0886	£716	0.1179	Ranibizumab dominates
Abbreviations: Dexamethasone, dexamethasone intravitreal implant; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Table 22. Scenario analyses for patients who had a pseudophakic lens (50% discount in list price of ranibizumab) [adapted from tables 201, 207, 208, 209, 210, 213, 219, and 220 on pages 478, 481, 482, 483, and 485 of company's submission]

Scenario	Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (cost per QALY)
Including other comparators	Laser	£8361	5.1368	-	-	-
	Beva	£9402	5.2377	£1041	0.1010	£10,310
	Rani (50% of list price)	£15,004	5.2066	£5602	-0.0312	Beva dominates (£95,180 vs. laser)
	Dexa	£15,720	5.0886	£6318	-0.1491	Beva dominates (-£152,857 vs. laser)
	Watch and wait	£21,823	4.9824	£12,421	-0.2553	Beva dominates (-£87,199 vs. laser)
Stable vision after discontinuing treatment	Dexa	£14,498	5.0981	-	-	-
	Rani	£14,718	5.2393	£219	0.1412	£1554
1 year time horizon	Dexa	£3555	0.5986	-	-	-
	Rani	£5966	0.6020	£2412	0.0035	£697,936
5 year time horizon	Dexa	£9456	2.5789	-	-	-
	Rani	£12,327	2.6390	£2871	0.0601	£47,729
10 year time horizon	Dexa	£13,132	4.2223	-	-	-
	Rani	£13,896	4.3233	£764	0.1010	£7564
100% unilateral DMO in WSE (no fellow eye involvement)	Dexa	£8134	5.1530	-	-	-
	Rani	£11,403	5.2099	£3269	0.0570	£57,384
All injections as day case	Dexa	£16,847	5.0886	-	-	-
	Rani	£18,773	5.2066	£1925	0.1179	£16,323
50% of injections as day case	Dexa	£16,284	5.0886	-	-	-
	Rani	£16,889	5.2066	£605	0.1179	£5128

Abbreviations: Beva, bevacizumab; Dexa, dexamethasone intravitreal implant; ICER, incremental cost effectiveness ratio; Inc., incremental; Laser, laser photocoagulation; Rani, ranibizumab; QALY, Quality adjusted life year.

ERG comments

5.32 The ERG stated that the sensitivity analyses conducted by the company were comprehensive.

5.33 The ERG highlighted that the FAME study used in the company's sensitivity analysis for patients who are insufficiently responsive to non-corticosteroid therapy had 2 major limitations. The study only reported the probability of gaining at least 15 letters, meaning that the probability of gaining at least 10 letters needed to be imputed in the model. Also, the study only reported 1 of the 3 outcomes of interest (gaining letters) and the remaining 2 outcomes needed to be imputed.

5.34 The ERG highlighted that increasing the duration of treatment from 3 to 5 years (scenarios 5 and 6) had no impact on the results in any population. However, they noted that this was due to limitations in the available data, as only 1 maintenance treatment per year (or a maximum of 1 additional fluocinolone acetonide 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.

5.35 The ERG did not agree that the scenarios with a time horizon less than 10 years (company's scenarios 9 and 10) were appropriate, as 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 had to made a number of assumptions to consider a time horizon of longer than 10 years (company's scenarios 11 and 12), as the data were only available for up to 3 years. The ERG noted that increasing the time horizon to 20 years (company's scenario 12) did not have any impact on the results.

5.36 The ERG did not believe that administering injections as day cases 100% or 50% of the time (scenarios 20 and 21) was relevant to UK clinical practice as their clinical expert informed them that the vast majority of dexamethasone intravitreal implant and anti-VEGF treatments would be administered in an outpatient setting.

Extra analyses carried out by the company in response to clarification

5.37 The ERG requested several additional analyses during clarification.

5.38 In the first analysis, the baseline BCVA distribution in bilateral diabetic macular oedema (DMO) was taken from the subgroup of patients with bilateral DMO, rather than from people with unilateral DMO (as in the base case). In this analysis, dexamethasone intravitreal implant remained cost-effective compared with watch and wait in DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy. In pseudophakic DMO patients, 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 £7,208 per QALY gained.

5.39 In the second analysis, the results of an updated NMA were used. The updated NMA included NCT00035906, which was excluded from the original NMA as it did not report data at 12 months. The results of the health economic analysis based on the updated NMA were very similar to the company's base case analysis. Scenario analyses including all relevant comparators were also presented by the company. Total costs and QALYs were marginally different from the values presented in the submission using the original NMA; however the difference was very small and the conclusion of the analyses remained unchanged.

5.40 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 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 NMA (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 NMA with the assumption that the 12-month relative risks remained constant to year 3. The ERG believed that this assumption was incorrect because the data from MEAD showed that the relative effect of dexamethasone intravitreal implant versus sham is not stable over 3 years. The ERG also argued that the differences in the economic analyses may be due to the company's normalization 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 NMA were more appropriate to use than the MEAD data as the sham arm of the MEAD studies was likely to over-estimate 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 NMA that provide relative effects for dexamethasone intravitreal implant compared with sham, and so these relative effects are also present in the results from the NMA. In the third analysis, the company restricted movements between health states to a maximum of one 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 who are unsuitable for or insufficiently responsive to non-corticosteroid therapy.

5.41 In the fifth and sixth analyses, the ERG requested the use of mean utilities for each health state were estimated directly from patients' responses in the MEAD trials. However, the company applied utility data from the MEAD trials in the model by linking the VFQ-UI data of each patient to all

patients' BSEs, and then, independently, to all patients' WSEs. This meant that the utility data for the BCVA health states of the BSE were affected by the BCVA of the WSE and vice versa. This resulted in the mean utility of the WSE appearing to be higher than the utilities of the BSE, which was not realistic. The ERG highlighted that this causes limitations in the approach, and did not consider these analyses further.

ERG exploratory analyses

5.42 The ERG identified and corrected the following potential errors in the company's model:

- The annual probability of fellow eye involvement in the model was [redacted]%, estimated from the 2 year probability of [redacted]%. This is an instantaneous rate and should have been converted to an annual probability of [redacted]% [analysis B1]
- The mean number of re-treatments for fluocinolone acetonide in year 3 in the model (0.26) was based on LOCF. However, cumulative data for year 3 available. The number of re-treatments in year 3 was estimated to be 0.036 [analysis B2]
- 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 has also been slightly amended from 2.34% to 2.32% [analysis B3]
- 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 [analysis B4]
- The cost of intermediate vitreous procedures used in the model was £1685. The ERG argued this should have been £989. The total cost of retinal detachment should have been £1080 as the ERG argued that the management of retinal detachment was estimated to be achieved

by intermediate vitreous procedure (day case) in 80% of cases and by major vitreous procedure (day case) in 20% of cases [analysis B5].

5.43 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 (DMO). For pseudophakic patients, ranibizumab remained dominant at 50% discount in 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 gave an ICER between £50,849 and £52,494 per QALY gained at the list price of ranibizumab.

5.44 The ERG also carried out the following scenario analyses:

- A higher annual probability of fellow eye involvement in years 1 and 2 (55.28%) [analysis C1]
- A higher 3-month probability of deterioration of vision by at least 10 letters for those ending or discontinuing treatment (5.5%) [analysis C2]
- Discontinuation rate of 0% for all treatments [analysis C3]
- Overall hazard ratio of mortality of 3.5 for DMO compared with the general population [analysis C4]
- Bilateral treatment with anti-VEGF was assumed to require 1 administration visit on 75% of occasions and 2 administration visits on 25% of occasions [analysis C5]
- Amendments to the total number of visits to account for some monitoring visits being incorporated into treatment visits (and not occurring separate monitoring costs) (see table 23 below) [analysis C6]
- Removed costs associated with intra-ocular pressure checks from the analysis as there are normally included in monitoring visits [analysis C7]
- Used the unit cost of private residential care (£532 per week) instead of the cost of local authority residential care (£10002 per week) for the annual costs of severe vision lost [analysis C8]

- Used the cost of depression from McCrone et al. after excluding the cost of residential care for the annual cost of severe vision loss [analysis C9]
- Mean cost of medication for raised IOP revised to £88.77. Calculated by using the unit cost of generic prostaglandins and assuming that 70% are treated with generic prostaglandins, 10% with generic beta-blockers and 20% by equal use of other treatments [analysis C10]
- The mean cost of surgical intervention for raised IOP was revised to £1273. Trabeculectomy was the only surgical procedure considered for the management of raised IOP. 50% of trabeculectomies were assumed to correspond to intermediate glaucoma day case procedures, and 50% to major glaucoma day case procedures [analysis C11]
- Additional IOP checks were assumed for patients who experience raised IOP. 2 extra IOP checks per year, over 3 years were assumed. The total cost of the 6 extra IOP checks was £480 [analysis C12]
- Utility data from Czoski-Murray et al. [analysis C13]

Table 23. Monitoring visits required for each treatment used in the ERG analyses [adapted from table 93 on page 231 of ERG report]

Treatment		Average number of treatments			Notes from the Evidence Review Group
		Year 1	Year 2	Year 3	
All diabetic macular oedema patients					
Dexa	Treatment	[redacted]	[redacted]	[redacted]	CS.
	Dedicated monitoring	[redacted]	[redacted]	[redacted]	CS; 1 extra visit assumed by ERG.
	Total	**5**	**4**	**4**	-
Watch and wait	Treatment	0	0	0	Not applicable.
	Dedicated monitoring	4	4	4	-
	Total	**4**	**4**	**4**	CS.
Flu ace	Treatment	1.00	0.26	0.036	CS; number for Year 3 corrected by ERG.
	Dedicated monitoring	4	3.74	3.964	CS; 1 extra visit assumed by ERG.
	Total	**5**	**4**	**4**	**-**
Diabetic macular oedema patients who have a pseudophakic lens					
Dexa	Treatment	[redacted]	[redacted]	[redacted]	CS.
	Dedicated monitoring	[redacted]	[redacted]	[redacted]	-
	Total	**5**	**4**	**4**	CS; 1 extra visit assumed by ERG.
Rani	Treatment	7.00	3.90	2.90	CS.
	Dedicated monitoring	6	4.10	3.10	-
	Total	**13**	**8**	**6**	TA274; 1 extra visit assumed by ERG (Year 1).
Beva	Treatment	9.00	4.00	2.90	CS.
	Dedicated monitoring	4	4	3.10	-
	Total	**13**	**8**	**6**	Assumed by company to equal to ranibizumab visits.
Laser	Treatment	[redacted]	[redacted]	[redacted]	CS.
	Dedicated monitoring	[redacted]	[redacted]	[redacted]	-
	Total	**5**	**4**	**4**	TA274; 1 extra visit assumed by ERG (Year 1).
Watch and wait	Treatment	0	0	0	Non-applicable.
	Dedicated monitoring	4	4	4	-
	Total	**4**	**4**	**4**	CS.

Abbreviations: Beva, bevacizumab; CS, company submission; Dexa, dexamethasone; ERG, evidence review group; Flu Ace, fluocinolone acetonide; Laser, laser photocoagulation; Rani, ranibizumab.

Note: monitoring visits assumed to incorporate treatment visits, with the exception of dexamethasone, fluocinolone acetate and laser, for which an extra treatment visit has been assumed

5.45 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.

5.46 The patients 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. 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.

5.47 The ERG 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 [analysis C5];
- 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 [analysis C6];
- costs associated with IOP checks were removed from the analysis, as IOP checks are performed within monitoring visits [analysis C7];
- the unit cost of local authority residential care was replaced by the unit cost of private residential care [analysis C8];
- the cost of depression, associated with severe vision loss, was updated using more recent data [analysis C9];

- 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 [analysis C10];
- 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 [analysis C11];
- 6 extra IOP visits were assumed for patients with DMO who were treated for raised IOP [analysis C12].

5.48 Following ERG corrections and amendments to the company's model data, the deterministic ICER of dexamethasone intravitreal implant versus watch and wait in patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, became £22,049 per QALY gained when NMA outputs were utilised; and £1,166,271 per QALY gained when data from the MEAD trials for both dexamethasone intravitreal implant and watch and wait (sham) were utilised, without transitions being restricted by one health state up or down, as shown in table 24. The ICER for patients who have a pseudophakic lens were £63,609 per QALY gained for ranibizumab compared with dexamethasone intravitreal implant, when the list price of ranibizumab was used (see table 26). When a 50% discount to the list price of ranibizumab was used, the ICER was £6162 per QALY gained for ranibizumab compared with dexamethasone intravitreal implant (see table 26). In a comparison with laser, bevacizumab, ranibizumab (at 50% discount) and watch and wait, bevacizumab and laser both dominated dexamethasone intravitreal implant (see table 27).

5.49 The results of the ERG's exploratory analysis are shown in tables 24 to 27. 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 12-month relative risks

and stable over the whole 3-year duration of treatment and the normalisation approach. The ERG therefore advised that the results obtained from these analyses should be interpreted with great caution.

Table 24. ERG's exploratory analyses results for patients who are unsuitable for, or insufficiently responsive to non-corticosteroids [adapted from tables 129 and 130 on pages 316 and 317 of the ERG report]

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Efficacy data based on MEAD trials (unrestricted moves between health states)					
Dexamethasone	£17,065	5.7589	£6727	0.0058	£1,166,271
Watch and wait	£10,338	5.7531	-	-	-
Efficacy data based on NMA (restricted moves between health states)					
Dexamethasone	£16,601	5.7438	£1428	0.0648	£22,049
Watch and wait	£15,174	5.6791	-	-	-
Abbreviations: Dexamethasone, dexamethasone intravitreal implant; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Table 25. ERG's exploratory analyses results for patients who are unsuitable for, or insufficiently responsive to non-corticosteroids; scenario including fluocinolone acetonide [adapted from table 131 on page 318 of ERG report and table 1 on page 2 of the ERG's additional analyses]

Technologies	Total		Incremental		ICER (per QALY gained)	ICER vs baseline
	Costs	QALYs	Costs	QALYs		
Fluocinolone acetonide at list price						
Watch and wait	£15,171	5.6791	-	-	-	-
Dexamethasone	£16,601	5.7438	£1431	0.0647	£22,105	£22,105
Flu ace	£20,170	5.8220	£3569	0.0781	£45,684	£35,000
Fluocinolone acetonide at 10% discount						
Dexamethasone	£16,601	5.7438	-	-	-	-
Flu ace	£19,183	5.8220	£2582	0.0781	£33,047	£33,047
Fluocinolone acetonide at 20% discount						
Dexamethasone	£16,601	5.7438	-	-	-	-
Flu ace	£18,196	5.8220	£1595	0.0781	£20,411	£20,411
Fluocinolone acetonide at 30% discount						
Dexamethasone	£16,601	5.7438	-	-	-	-
Flu ace	£17,209	5.8220	£607	0.0781	£7775	£7775
Fluocinolone acetonide at 40% discount						
Dexamethasone	£16,601	5.7438	-	-	-	-
Flu ace	£16,222	5.8220	-£380	0.0781	Flu ace dominates	Flu ace dominates
Fluocinolone acetonide at 50% discount						
Watch and wait	£15,171	5.6791	-	-	-	-
Flu ace	£15,235	5.8220	£64	0.1428	£446	£446
Dexamethasone	£16,601	5.7438	£1367	-0.0781	Flu ace dominates	£22,105

Abbreviations: Dexamethasone, dexamethasone intravitreal implant; Flu ace, fluocinolone acetonide; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 26. ERG's exploratory analyses for patients who have a pseudophakic lens; efficacy data based on network meta-analysis [adapted from table 132 on page 318 of the ERG report and table 2 on page 3 of the ERG's additional analyses]

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Ranibizumab list price					
Dexamethasone	£12,841	5.0894	-	-	-
Ranibizumab	£20,219	5.2054	£7378	0.1160	£63,609
Ranibizumab 10% discount price					
Dexamethasone	£12,841	5.0894	-	-	-
Ranibizumab	£18,886	5.2054	£6045	0.1160	£52,119
Ranibizumab 20% discount price					
Dexamethasone	£12,841	5.0894	-	-	-
Ranibizumab	£17,554	5.2054	£4713	0.1160	£40,630
Ranibizumab 30% discount price					
Dexamethasone	£12,841	5.0894	-	-	-
Ranibizumab	£16,221	5.2054	£3380	0.1160	£29,141
Ranibizumab 40% discount price					
Dexamethasone	£12,841	5.0894	-	-	-
Ranibizumab	£14,888	5.2054	£2047	0.1160	£17,651
Ranibizumab 50% discount price					
Dexamethasone	£12,841	5.0894	-	-	-
Ranibizumab	£13,556	5.2054	£715	0.1160	£6162
Abbreviations: Dexamethasone, dexamethasone intravitreal implant; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Table 27. ERG's exploratory analyses for DMO patients who have a pseudophakic lens; scenario including laser, bevacizumab and watch and wait [adapted from table 133 on page 319 of the ERG report]

Intervention	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (per QALY gained)
Laser	£6831	5.1369	-	-	-
Bevacizumab	£7915	5.2359	£1084	0.0990	£10,945
Dexamethasone	£12,841	5.0894	£4926	-0.1465	Bevacizumab dominates (-£126,595 vs. laser)
Ranibizumab (50% of list price)	£13,556	5.2054	£5640	-0.0305	Bevacizumab dominates (£98,134 vs. laser)
Watch and wait	£14,799	4.9847	£6883	-0.2512	Bevacizumab dominates (-£52,356 vs. laser)
Abbreviations: Dexamethasone, dexamethasone intravitreal implant; ICER, incremental cost-effectiveness ratio; Incr., incremental; Laser, laser photocoagulation; QALYs, quality-adjusted life years.					

6 Innovation

6.1 Justifications for considering dexamethasone intravitreal implant to be innovative:

- Dexamethasone intravitreal implant requires less injections than anti-VEGF treatments. This represents a considerable advantage to patients, carers and the health service which is unlikely to be captured within the QALY calculation.

7 Equality issues

7.1 No potential equality issues were identified in the evidence submitted by the company, the ERG report or the patient and expert statements.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

The EPAR for dexamethasone intravitreal implant (Ozurdex) can be found on the European Medicines Agency website using the link below.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001140/WC500095499.pdf