



TA301 Manufacturer's submission and committee papers

Other supporting evidence

Published: 13 March 2024

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1 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of fluocinolone acetonide intravitreal implant and a review of this submission by the Evidence Review Group (ERG; [section 4](#)).

- 1.1 The manufacturer submitted evidence on the clinical and cost effectiveness of fluocinolone acetonide intravitreal implant compared with optimised standard of care and laser photocoagulation monotherapy. The manufacturer did not provide any specific analyses comparing fluocinolone acetonide intravitreal implant with triamcinolone alone or the anti-vascular endothelial growth factor (anti-VEGF) treatments bevacizumab and ranibizumab alone.
- 1.2 The main source of evidence in the manufacturer's submission was a preplanned analysis of data from the FAME A and B randomised controlled trials that evaluated the safety and efficacy of fluocinolone acetonide intravitreal implant for treating diabetic macular oedema. The preplanned analysis focused on duration of diabetic macular oedema, analysing patients who had had the condition for durations above and below the median separately. When the trial was unblinded the median duration was determined to be 3 years. The subgroup in the submission was patients with duration of diabetic macular oedema over 3 years (the manufacturer calculated the duration of diabetic macular oedema as the year of randomisation to treatment minus the year of diagnosis of the disease plus 1).
- 1.3 FAME A and B were 2 identical, randomised, double-blinded, sham injection-controlled multicentre trials conducted over 36 months. The results of the trials were combined and presented in the submission as a single analysis. Patients were randomised 1:2:2 to sham injection, 0.2 micrograms/day (low-dose) or 0.5 micrograms/day (high-dose) fluocinolone acetonide intravitreal implant. Participants in the trials were adults with diabetic macular oedema who were aged between 18 and 85, who had received at least 1 previous laser treatment, whose best corrected visual acuity (BCVA) was 19 to 68 letters on the Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart, and whose central retinal thickness was 250 microns or more at baseline. Exclusion criteria were intraocular pressure over 21 mmHg, and systolic blood pressure over 180 mmHg

or diastolic blood pressure over 105 mmHg.

- 1.4 In both groups (sham injection and low- or high-dose implant) additional treatment with laser photocoagulation was given as needed after week 6. Approximately 61% of the sham injection group and 41% of the fluocinolone acetonide intravitreal implant group received treatment with laser photocoagulation during the study. The mean number of laser treatments was 1.4 and 0.8 in the sham injection and fluocinolone acetonide intravitreal implant groups respectively. Re-treatment with fluocinolone acetonide intravitreal implant was offered at any time after the month 12 assessments if patients experienced vision loss (5 letters or more) or retinal thickening of 50 microns or more compared with their best status in the previous 12 months.
- 1.5 Patients in both groups also received a range of therapies not allowed in the study protocol. These included intravitreal steroids (triamcinolone and dexamethasone), anti-VEGF therapy, vitrectomies and posterior sub-Tenon steroids. The number of off-protocol treatments was higher in the sham injection group than in the fluocinolone acetonide intravitreal implant group (117 compared with 48); approximately 35% of patients in the sham injection group and 13% of patients in the fluocinolone acetonide intravitreal implant group received at least 1 off-protocol treatment. Data from these patients were included in the analysis population.
- 1.6 The primary outcome reported in the FAME trials was the proportion of people with an improvement of 15 or more letters from baseline BCVA at month 24. Secondary outcomes included:
- mean change in BCVA
 - mean change in excess retinal thickness
 - percentage with 3-step (15 letters or more) worsening of ETDRS
 - percentage needing laser photocoagulation.
- 1.7 There were 956 patients enrolled in the FAME trials. Of these, 536 formed the subgroup of patients with chronic diabetic macular oedema for longer than 3 years. Of this subgroup of patients comprehensive data were presented by the manufacturer for the 0.2 micrograms/day implant group only, because only the

low dose has been licensed. The resulting number of patients with chronic diabetic macular oedema in the subgroup that formed the basis of the manufacturer's submission was 321 (209 in the 0.2 micrograms/day implant group and 112 in the sham injection group).

- 1.8 The mean age of the patients was 62.9 years in the sham injection group (n=112) and 63.7 years in the 0.2 micrograms/day implant group (n=209). In the trials, the majority of patients had chronic diabetic macular oedema in both eyes at baseline, but only 1 eye was treated. In most cases, the worse-seeing eye was treated.
- 1.9 At month 24, the proportions of patients with chronic diabetic macular oedema who had a 15.0 letters or more increase from baseline BCVA were 13.4% and 34.4% in the sham injection and 0.2 micrograms/day implant groups respectively ($p < 0.001$). The proportions of patients who had a 15.0 letters or more improvement in BCVA at month 36 (13.4% and 34.0% respectively [$p < 0.001$]) were comparable to those observed in month 24. There were numerical increases in mean change in BCVA from baseline in the 0.2 micrograms/day implant group compared with the sham injection group at all evaluations (12 through to 36 months); this was statistically significant at months 30 and 36. At month 36, there was a mean improvement of 7.6 letters in the 0.2 micrograms/day implant treatment group compared with 1.8 letters in the sham injection group ($p < 0.004$).
- 1.10 The FAME trials included an assessment of health-related quality of life using the Visual Function Questionnaire-25 (VFQ-25) at baseline and months 24 and 36. These data were provided in the clinical study reports of the FAME trials. The manufacturer stated that the VFQ-25 was not used in the economic model because it measures overall visual function which is driven by vision in the better-seeing eye, whereas in the FAME trials, the majority of patients had their worse-seeing eye treated. The VFQ-25 values are marked by the manufacturer as academic in confidence and therefore not presented here.
- 1.11 The manufacturer also included laser photocoagulation monotherapy as a relevant comparator for fluocinolone acetonide intravitreal implant. The manufacturer conducted a literature search and identified 1 relevant study: DRCR Protocol B (2008). This study was a phase 3, multicentre, randomised clinical trial conducted in the USA to compare intravitreal triamcinolone with focal/grid laser

photocoagulation in patients with diabetic macular oedema. The manufacturer noted that the severity of diabetic macular oedema in the DRCR study was not as great as in the FAME trials. Of the DRCR population, approximately 40% of people had not had their disease treated with laser and there was no stipulation on duration of diabetic macular oedema at randomisation. A comparison of outcomes data as reported in the DRCR and FAME clinical trials was presented. The manufacturer did not use any statistical methods to compare the data indirectly. The manufacturer noted that the proportion of people with a 15 letters or more improvement in BCVA in the FAME trials at month 36 demonstrated a numerical difference in favour of fluocinolone acetonide intravitreal implant (34.0% compared with 18% for laser photocoagulation at 24 months in the DRCR Protocol B study).

- 1.12 The manufacturer's submission included data from the FAME trials for ocular adverse events in people with chronic diabetic macular oedema (duration of 3 years or longer). The data suggested that fluocinolone acetonide intravitreal implant is associated with the formation or progression of cataract and increased intraocular pressure. In the FAME trials, 34.4% (72/209) of patients in the fluocinolone acetonide intravitreal implant group experienced increased intraocular pressure or ocular hypertension compared with 14.3% (16/112) in the sham injection group. At baseline, 58.9% (66/112) of people in the sham injection group and 54.5% (114/209) in the fluocinolone intravitreal implant group were phakic (still had their natural lens). Of those who were phakic at baseline, 77.9% of the fluocinolone acetonide intravitreal implant group and 77.0% of the sham injection group had a pre-existing cataract. Cataract surgery was needed by 85.1% (97/114) of the fluocinolone acetonide intravitreal implant group and 36.4% (24/66) of the sham injection group who were phakic at baseline.
- 1.13 The manufacturer provided a subgroup analysis of people with chronic diabetic macular oedema who had treatment in an eye with a pseudophakic lens (that is, they had already had an operation for cataract removal and had been fitted with an intraocular lens to replace the natural crystalline lens) at entry into the FAME trials. The manufacturer considered the overall treatment effect in this subgroup to be similar to that for the phakic population; however, increased benefits arose through the removal of a known adverse event (advancement of cataract development) and removal of the costs associated with cataract surgery. Of the people with chronic diabetic macular oedema, there were 46 (41.1%) who had a

pseudophakic lens in the sham injection group and 95 (45.5%) in the 0.2 micrograms/day fluocinolone-treated group. For this subgroup, at 36 months, 31.6% in the fluocinolone-treated group and 17.4% in the sham injection group had a greater than 15-letter increase from baseline BCVA, giving a difference of 14.2% (95% CI 28.6% to -0.2%).

- 1.14 The economic evidence provided by the manufacturer in its submission comprised a literature review (which identified no relevant published cost-effectiveness studies) and a de-novo cost-utility analysis. The manufacturer's economic evaluation compared fluocinolone acetonide intravitreal implant with the comparator ('optimised standard of care') in the FAME trials for a cohort of patients with chronic diabetic macular oedema. The model also included a comparison of fluocinolone acetonide intravitreal implant with laser photocoagulation using data for laser photocoagulation from the DRCR Protocol B study.
- 1.15 The manufacturer's model included 14 health states (13 BCVA health states and death) which were defined by bands of 5 ETDRS letters in the treated eye. Utility values associated with the 13 BCVA-related health states captured the effect of varying degrees of visual gain or loss on patients' quality of life. The model structure made no distinction between treatment of the better-seeing eye and the worse-seeing eye. The model had a 15-year time horizon and a quarterly cycle length, with costs and benefits both being discounted at 3.5%. For the first 3 years, the distribution of patients across health states was drawn directly from the FAME trials data. Beyond 3 years, a Markov model structure was adopted with transition probabilities being applied.
- 1.16 The base-case analysis assumed that 1 fluocinolone acetonide intravitreal implant is needed every 3 years. Patients needed to have gained 5 or more ETDRS letters of visual acuity between baseline and month 36 to receive a further implant at month 36. In addition, using data from the FAME trials the manufacturer applied a drop-out rate (for those who withdrew consent, were lost to follow-up or died) to the patients receiving fluocinolone acetonide intravitreal implant who were re-treated at the end of the first 36 months (these details are marked by the manufacturer as commercial in confidence and therefore not presented here). This adjusted re-treatment rate was applied equally to each health state. Patients in both the fluocinolone group and the optimised standard of care group also

received laser treatments based on rates from the FAME trials, and in the first 3 years could receive other therapies including triamcinolone, ranibizumab, bevacizumab and dexamethasone, again based on rates in the FAME trials.

- 1.17 In the base-case analysis, it was assumed that 35% of patients would receive bilateral treatment in the optimised standard of care group. The manufacturer assumed that bilateral treatment would be contraindicated for patients treated in the first eye with fluocinolone acetonide intravitreal implant who had a subsequent rise in intraocular pressure greater than 30 mmHg. Therefore the bilateral treatment rate in the fluocinolone group was reduced based on the proportion of patients with raised intraocular pressure observed in the FAME trials.
- 1.18 The clinical efficacy data from the FAME trials were used directly to calculate the number of patients in each of the model health states in each quarter for the first 3 years. Changes after 3 years were extrapolated from the FAME trials data. The FAME data were divided into patients whose disease had responded to and not responded to treatment based on the ETDRS 5-letter criteria. Data were then analysed to determine the numbers of patients whose vision improved or worsened by at least 5 letters each quarter. The average net changes in the last 4 quarters of the FAME trials were used in the model to extrapolate improvements in vision beyond 3 years. For patients receiving another implant at 36 months, the model assumed that 5% of patients in each health state would improve by 5 letters every quarter. For patients not receiving a further implant at 36 months, the model assumed that 3% of patients in each health state would experience a transition to a lower health state every quarter. In the optimised standard of care group and laser group, the model assumed that 3% of patients in each health state would have a worsening in vision of 5 letters and therefore move to a worse health state every quarter.
- 1.19 The manufacturer did not consider it appropriate to include the VFQ-25 values in the economic model because VFQ-25 is driven by vision in the better-seeing eye, whereas in the FAME trials, the majority of patients had their worse-seeing eye treated (these values are marked by the manufacturer as academic in confidence and are therefore not presented here). Furthermore, the manufacturer stated that a mapping exercise was not considered because there was not a universally accepted mapping process to convert VFQ-25 data to utility scores.

- 1.20 The manufacturer conducted a systematic review to identify utility values reported in the literature for populations with visual impairment. The review of the articles included diabetic macular oedema and other disorders affecting visual acuity (such as age-related macular degeneration). Based on the data available, the manufacturer chose to use time trade-off data from Brown et al. (2000) as the source of utility values for its submission. Brown et al. (2000) was a US study that measured utility values in 5 groups according to visual acuity in the better-seeing eye in a population of patients with age-related macular degeneration. The values estimated by Brown et al. (2000) and the values used within the model ranged from 0.40 in the lowest health state (less than 20 ETDRS letters) to 0.89 in the highest health state (75 ETDRS letters or more). The Brown et al. (2000) study did not report utility weights in patients with BCVAs between 35 and 50, and therefore the unweighted averages of the utility weights above and below this range were assumed.
- 1.21 For patients who received treatment in both eyes, a 25% bilateral treatment quality-adjusted life year (QALY) uplift was also applied to the aggregate QALYs.
- 1.22 The model did not consider utility decrements due to adverse events, or procedures and interventions for the adverse events. The manufacturer stated that because the utility was calculated for BCVA values, and the BCVA values were based on the trial data, the impact on patient vision of adverse events such as cataract formation was reflected in the BCVA of the treated eye.
- 1.23 The model included the costs of fluocinolone acetonide intravitreal implant as well as laser and other therapies at the rates observed in the FAME trials. Adverse event costs were also included. The manufacturer applied an annual cost of blindness of £6298 to the proportion of patients whose treated-eye BCVA fell below 35 letters.
- 1.24 In its deterministic base case, based on an incremental cost of £11,330 and an incremental QALY value of 0.500, the manufacturer estimated an incremental cost-effectiveness ratio (ICER) without the patient access scheme of £22,655 per QALY gained for fluocinolone acetonide intravitreal implant compared with optimised standard of care.
- 1.25 Following a request for clarification from the ERG the manufacturer provided a

revised analysis. The manufacturer acknowledged that the health-related quality of life values from Brown et al. (2000) may not apply to patients having their worse-seeing eye treated. The manufacturer therefore used revised health-related quality of life values to reflect a weighted average of values for people having their worse- and better-seeing eyes treated, taken from a study by Heintz et al. (2012).

- 1.26 As well as changing health-related quality of life values, the manufacturer's revised analysis also amended: male and female mortality rates to revise the pooled annual all-cause mortality risk, the proportion of patients needing bilateral treatment, the percentage of patients needing bilateral treatment and for whom a second fluocinolone acetonide intravitreal implant treatment was not contraindicated, the quality of life uplift from bilateral treatment to 10%, and the unadjusted response rate in the fluocinolone group to a rate based upon a 10-letter re-treatment criterion.
- 1.27 The manufacturer's amendments reduced the estimate of cost effectiveness for fluocinolone acetonide intravitreal implant compared with optimised standard of care from £22,655 to £19,268 per QALY gained without the patient access scheme, based on an incremental cost of £11,927 and an incremental QALY value of 0.619.

ERG comments on the manufacturer's submission

- 1.28 The ERG commented that the 3-year data used to inform the first 3 years of the economic model were robust, although the more usual modelling approach would have been to use transition probability matrices. The structure of the model means it cannot be manipulated during this 3-year period to explore different scenarios.
- 1.29 The ERG commented that it would have been more appropriate for the manufacturer to use a model structure that modelled patients as having 2 eyes, rather than undertaking an ad hoc adjustment to the output of a model in which patients only had 1 eye. The ERG noted that the FAME trials had a reasonable proportion of patients who had their better-seeing eye treated, and that the rate of chronic diabetic macular oedema in the other eye was high.

- 1.30 The ERG also noted that the distribution between health states for patients whose disease had responded to and not responded to fluocinolone acetonide intravitreal implant at 36 months was modelled as being a constant percentage of the overall patient distribution at 36 months. The ERG commented that this approach was not justified, and could lead to bias in the estimates of cost effectiveness for fluocinolone acetonide intravitreal implant.
- 1.31 The ERG noted that the manufacturer's base-case model applied a re-treatment criterion of a minimum 5-letter improvement between baseline and 36 months. The ERG commented that a more realistic criterion might be a minimum 10-letter improvement between baseline and 36 months, which the manufacturer applied in response to the clarification request from the ERG. However, the ERG commented that this only changed the number of patients not receiving another fluocinolone acetonide intravitreal implant at 36 months and did not affect their distribution across health states.
- 1.32 In the manufacturer's submission clinical effectiveness beyond 3 years was extrapolated from the FAME trials data. The ERG commented that rather than including the proportions of patients whose disease improved or worsened each quarter of a year, the proportions were netted. The ERG considered that the reasons for analysing the data in this way were unclear.
- 1.33 The ERG commented that because in the FAME trials patients had only 1 eye treated, assumptions were needed about rates of bilateral treatment. In the base-case analysis, it was assumed that 35% of patients would need bilateral treatment; this percentage was increased in the revised analysis (these details are marked by the manufacturer as academic in confidence and therefore not presented here). The ERG considered that the manufacturer's revision was too high because a proportion of patients would not have visual impairment in both eyes because of diabetic macular oedema, and a proportion would not be able to have both eyes treated because of raised intraocular pressure or other reasons.
- 1.34 The ERG commented that there was considerable uncertainty about the appropriateness of the utility values used in the model. The original submission used utility values that related to sight in the better-seeing eye. The ERG considered there were limitations in the data (based on Heintz et al. 2012) used in the revised analysis because these provided only 3 quality of life values over

13 health states, were based on small patient numbers, and were non-monotonic.

Exploratory analyses by the ERG

1.35 Initially, the ERG made a series of revisions to address what it considered to be possible errors in the model. These were:

- a change to the formulae for averaging mortality between male and female rates
- a change to the formulae for applying the yearly natural discontinuation rate (the detail of which is commercial in confidence) in the cohort flow cells
- a change to the formula for the percentage of patients remaining on fluocinolone acetonide intravitreal implant after year 9.

The cumulative impact of correcting the 3 errors was to increase the ICER without the patient access scheme from £22,655 to £26,526 per QALY gained for fluocinolone acetonide intravitreal implant compared with optimised standard of care.

1.36 The ERG also conducted additional exploratory analyses changing:

- how the cost of fluorescein angiography needed before each laser administration was applied in the model
- the number of laser administrations per patient
- the unit costs for adverse event procedures
- how the proportions of people whose disease improved and worsened each quarter year after 36 months was calculated
- the rate of bilateral treatment
- the cost of blindness
- the cost and quality of life uplift applied for bilateral treatment for patients in the fluocinolone group whose condition needed bilateral treatment but for

whom a second implant was contraindicated.

The cumulative impact of these changes resulted in ICERs of £37,740 for the 5-letter response criterion (with an incremental cost of £14,569 and an incremental QALY of 0.386) and £35,940 for the 10-letter response criterion (with an incremental cost of £12,736 and an incremental QALY of 0.354) without the patient access scheme.

- 1.37 The ERG also conducted further exploratory sensitivity analyses with a particular focus on the source of utility values. These additional analyses modelled the impact of changes in the BCVA of the better-seeing eye using Brown et al. (1999). This US study of 325 patients measured utility values in 12 groups according to visual acuity in the better-seeing eye in a population of patients with impaired vision in at least 1 eye. The values estimated by Brown et al. (1999) used within the model vary from 0.54 in the lowest health state (less than 20 ETDRS letters) to 0.89 in the highest health state (75 ETDRS letters or more), giving a range of 0.350 across the health states of the model. The ERG commented that if its cost-effectiveness estimates without the patient access scheme for fluocinolone acetonide intravitreal implant compared with optimised standard of care were used as a starting point (£37,740 per QALY gained for the 5-letter response criterion and £35,940 per QALY gained for the 10-letter response criterion), applying the health-related quality of life values taken from Brown et al. (1999) would suggest cost-effectiveness estimates of £66,744 per QALY gained (5-letter response criterion) and £64,249 per QALY gained (10-letter response criterion).
- 1.38 The ERG explored the effect of using health-related quality of life values from a regression analysis in the manufacturer's submission for NICE's technology appraisal guidance 237 on ranibizumab for the treatment of diabetic macular oedema (replaced by [NICE's technology appraisal guidance 274 on ranibizumab for the treatment of diabetic macular oedema](#)), and from Brown et al. (1999) and Brown et al. (2000). The ERG noted that there was uncertainty around the health-related quality of life impact resulting from changes in the BCVA of the worse-seeing eye, and presented 6 scenario analyses to take this into account in conjunction with the 3 different sources of utility values:
- Scenario analysis 1: A flat health-related quality of life function where

changes in the BCVA of the worse-seeing eye have no impact.

- Scenario analysis 2: A health-related quality of life function where changes in the BCVA of the worse-seeing eye have 15% of the range of changes in the BCVA of the better-seeing eye: that is, a range of 15% of 0.350 which equals 0.053.
- Scenario analysis 3: A health-related quality of life function where changes in the BCVA of the worse-seeing eye have 30% of the range of changes in the BCVA of the better-seeing eye: that is, a range of 30% of 0.350 which equals 0.105.
- Scenario analysis 4: A health-related quality of life function where changes in the BCVA of the worse-seeing eye have 50% of the range of changes in the BCVA of the better-seeing eye: that is, a range of 50% of 0.350 which equals 0.175.
- Scenario analysis 5: A health-related quality of life function where changes in the BCVA of the worse-seeing eye have 70% of the range of changes in the BCVA of the better-seeing eye: that is, a range of 70% of 0.350 which equals 0.245.
- Scenario analysis 6: A health-related quality of life function where changes in the BCVA of the worse-seeing eye have 100% of the range of changes in the BCVA of the better-seeing eye: that is, a range of 0.350.

1.39 The ERG also assumed that 20% and 40% of people received unilateral treatment in their better-seeing eye and worse-seeing eye respectively. For the fluocinolone group it was further assumed that 34% of people received bilateral treatment with fluocinolone acetonide intravitreal implant (that is, in both eyes), whereas 6% received treatment with fluocinolone acetonide intravitreal implant in the first eye but not in the second eye. In the optimised standard of care group, the ERG similarly assumed that 20% and 40% of people received unilateral treatment in their better-seeing and worse-seeing eye respectively; whereas 40% of people were assumed to receive treatment in both eyes.

1.40 The ERG completed sensitivity analyses without the patient access scheme. Using Brown et al. (1999), the ICERs (based on a 10-letter response criterion and including a bilateral benefit) ranged from £48,533 per QALY gained (scenario

analysis 6, where changes in the BCVA of the worse-seeing eye have 100% of the range of changes in the BCVA of the better-seeing eye, that is, a range of 0.350) to £110,730 per QALY gained (scenario analysis 1, where changes in the BCVA of the worse-seeing eye are assumed to have no impact). Using Brown et al. (2000), the equivalent ICERs ranged between £30,910 and £61,942 per QALY gained for fluocinolone acetonide intravitreal implant compared with optimised standard of care. Using the utility values derived from the manufacturer's submission for NICE's technology appraisal guidance 237 on ranibizumab for the treatment of diabetic macular oedema, based upon the 10-letter response criterion and including a bilateral benefit, the ICERs ranged from £69,802 (scenario analysis 6) to £251,686 per QALY gained (scenario analysis 1). Using a 10-letter response criterion, including a bilateral benefit and assuming scenario analysis 3 the ICER values were £47,604 per QALY gained using Brown et al. (2000) utilities and £80,037 per QALY gained using Brown et al. (1999) utilities.

- 1.41 Full details of all the evidence are in the manufacturer's submission and the ERG report for [NICE technology appraisal guidance 271 on fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy](#).

Rapid review of NICE technology appraisal guidance 271: patient access scheme

- 1.42 In NICE's technology appraisal guidance 271, fluocinolone acetonide intravitreal implant was not recommended for treating chronic diabetic macular oedema. After publication, the manufacturer agreed a patient access scheme with the Department of Health and submitted revised analyses to be considered in a rapid review of the original guidance.
- 1.43 The manufacturer presented analyses for the full population of people with chronic diabetic macular oedema and for the subgroup of people with chronic diabetic macular oedema who had treatment in an eye with a pseudophakic lens. In the revised economic model the manufacturer included:
- BCVA patient distributions in the extrapolation from month 36 onwards that were specific to a patient's response status

- BCVA patient distributions in the extrapolation for the pseudophakic subgroup that were based on the final 30 months of observations from the FAME trials, and BCVA patient distributions for the full chronic diabetic macular oedema population that were based on the final 12 months of observations
- analyses using utility values from Brown et al. (1999) and Brown et al. (2000), as well as an analysis using utilities from Czoski-Murray et al. (2009) (used in NICE's technology appraisal guidance 237 on ranibizumab for the treatment of diabetic macular oedema, replaced by [technology appraisal guidance 274 on ranibizumab for treating diabetic macular oedema](#))
- an assumption that changes in vision for people treated in their worse-seeing eye had 30% of the health-related quality of life impact of the same change in vision from treating their best-seeing eye
- an assumption that 20% of patients are unilaterally treated in the best-seeing eye, 40% of patients are unilaterally treated in the worst-seeing eye, and the remaining 40% of patients receive bilateral treatment.

1.44 The manufacturer also clarified some characteristics of the people enrolled in the FAME trials. It stated that people in the trials were as severely affected as patients who would receive fluocinolone acetonide intravitreal implant in routine clinical practice. It stated that in clinical practice, a BCVA of 20/80 is generally considered poor and insufficiently responsive to treatment. It noted that in the FAME trials 59% of the patients with chronic diabetic macular oedema had vision of 20/80 or worse at baseline. Of these, 42.7% and 12.7% of patients had a 15-letter gain in the fluocinolone acetonide intravitreal implant and optimised standard of care groups respectively ($p < 0.001$). The manufacturer also stated that in the FAME trials all patients had at least 1 prior macular laser treatment before randomisation. It noted that in the optimised standard of care group, people with diabetic macular oedema for more than 3 years showed lower levels of response (13.4% of patients) than people with diabetic macular oedema for less than 3 years (27.8% of patients); whereas in the fluocinolone acetonide intravitreal implant group, people with diabetic macular oedema for more than 3 years showed higher levels of response (34% of patients) than people with diabetic macular oedema for less than 3 years (22.3% of patients). The manufacturer considered that fluocinolone acetonide intravitreal implant provided

significant additive benefit for people with chronic diabetic macular oedema whose disease was responding insufficiently to other therapies.

- 1.45 The manufacturer presented the results for the comparison between fluocinolone acetonide intravitreal implant and optimised standard of care with the patient access scheme for the whole population with chronic diabetic macular oedema and for the subgroup of people with a pseudophakic lens. The ICERs for the whole population with the patient access scheme were £37,630 using the utilities from Brown et al. (2000) and £63,472 using the utilities from Brown et al. (1999) per QALY gained. The ICER using the utilities from Czoski-Murray et al. (2009) was £42,663 per QALY gained. In the pseudophakic subgroup the ICERs were £17,639 using the utilities from Brown et al. (2000) and £30,296 using the utilities from Brown et al. (1999) per QALY gained. Using the utilities from Czoski-Murray et al. (2009) the ICER was £19,884 per QALY gained.
- 1.46 The manufacturer carried out a sensitivity analysis assuming that patients would not be re-treated with fluocinolone acetonide intravitreal implant automatically at month 36. Re-treatment would only take place if there was a response to treatment and a BCVA less than 20/32 at month 36. These analyses resulted in small reductions in the ICERs. With the patient access scheme, the ICERs for the chronic diabetic macular oedema population were £34,668 using utilities from Brown et al. (2000) and £57,476 using utilities from Brown et al. (1999) per QALY gained. In the pseudophakic subgroup, the ICERs were £16,642 using the utilities from Brown et al. (2000) and £28,584 using the utilities from Brown et al. (1999) per QALY gained.

Comments on the manufacturer's rapid review submission by the Evidence Review Group

- 1.47 The ERG stated that there continued to be uncertainty about the best source of utilities to be used in the model. It noted that utilities from Brown et al. (1999) represented a more diverse group of patients with different eye conditions, all of whom were visually impaired with vision of at best 20/40 in at least 1 eye. The ERG considered that utilities from Brown et al. (1999) may be preferable to those from Brown et al. (2000) because Brown et al. (1999) included more patients,

which allows a finer gradation of utility estimates for a given BCVA. The number of patients for a given BCVA band was also higher in Brown et al. (1999). The ERG also noted that one-third of patients in Brown et al. (1999) had diabetes compared with none in Brown et al. (2000).

- 1.48 The ERG commented that it was unable to source the utility values from Czoski-Murray et al. (2009) used by the manufacturer. The ERG applied the Czoski-Murray utility function adjusted for an average age of 63 and found similar ranges to those used by the manufacturer. The ERG noted that patients included in Czoski-Murray et al. (2009) used contact lenses to simulate different degrees of visual loss. It also noted that the duration of the simulated visual impairment was short, and so the utility values may not apply to patients with longer duration of visual loss.
- 1.49 The ERG commented that the differences between the ICERs for the whole chronic diabetic macular oedema population and the pseudophakic subgroup were in part driven by differences in the distribution of patients across health states. The ERG noted that there were uncertainties around these distributions because for the pseudophakic subgroup, the difference in the baseline distributions between the fluocinolone group and the optimised standard of care group may indicate a breakdown in randomisation. It also noted that there were differences in the 36-month patient distributions within the optimised standard of care group, between the full chronic diabetic macular oedema population and the pseudophakic subgroup. The ERG commented on the importance of these patient distributions because they are the basis for the extrapolations in the model.
- 1.50 The ERG checked the manufacturer's ICERs and found minor differences in the values. The ERG commented that there were some small changes made to response rates and drop-out rates that had not been previously applied in the model. The ERG also commented that there were some errors in the adverse effect cost calculations, but correcting for these had little impact on the ICERs. The deterministic ICERs from the ERG check with the patient access scheme for the chronic diabetic macular oedema population were £64,549 and £37,996 per QALY gained using Brown et al. (1999) and Brown et al. (2000) utilities respectively. For the pseudophakic subgroup, the ICERs with the patient access scheme were £30,025 (using Brown et al. [1999] utilities), £21,027 (using Czoski-Murray utilities) and £17,487 (using Brown et al. [2000] utilities) per QALY

gained.

- 1.51 The ERG noted that the manufacturer presented a sensitivity analysis that assumed that patients would be re-treated at month 36 only if their disease responded to fluocinolone and they had a BCVA of less than 20/32. The ERG commented that this change only affected costs in the fluocinolone acetonide intravitreal implant group without any clinical impact of these patients stopping treatment. It also stated that the impact on costs may be underestimated as the re-treatment adjustment was only applied to the second re-treatment with fluocinolone acetonide intravitreal implant (at month 36) but not to subsequent re-treatments.

2 Consideration of the evidence

- 2.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of fluocinolone acetonide intravitreal implant, having considered evidence on the nature of chronic diabetic macular oedema after an inadequate response to prior therapy and the value placed on the benefits of fluocinolone acetonide intravitreal implant by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 2.2 The Committee discussed the causes of diabetic macular oedema, and recognised the importance of good control of blood glucose, blood pressure and blood lipids in reducing the risk of diabetic macular oedema, the progression of diabetic macular oedema and other complications. The Committee discussed the impact of visual impairment on people with diabetic macular oedema. It was aware of comments from patient experts describing the significant negative impact that visual impairment has on the physical and emotional wellbeing of people with diabetic macular oedema. The Committee noted that people with diabetes manage some aspects of their own condition and that visual impairment can affect their ability to do this. This in turn can increase the risk of long-term disease complications such as kidney disease, cardiovascular disease and amputations. The Committee also heard from clinical specialists that chronic diabetic macular oedema tends to be a bilateral condition (that is, affecting both eyes) with the potential risk of losing sight in both eyes. The clinical specialists stated that chronic diabetic macular oedema therefore affects the quality of life of people with the condition by causing visual impairment and also that of their carers because of loss of independence. The Committee noted comments from clinical specialists which highlighted that several studies have reported depression in people with chronic diabetic macular oedema. The Committee recognised the impact of visual impairment on people with diabetic macular oedema, particularly those with chronic diabetic macular oedema that is not responsive to available therapies.
- 2.3 The Committee discussed the current management of diabetic macular oedema. The Committee was aware that [NICE technology appraisal guidance 274 on ranibizumab for treating diabetic macular oedema](#) is the only NICE guidance

relating specifically to treating diabetic macular oedema. It noted that the marketing authorisation for fluocinolone acetonide intravitreal implant specified its use only when diabetic macular oedema was insufficiently responsive to available therapies and that this population was not covered by NICE technology appraisal guidance 274. The Committee heard from the clinical specialists that when anti-vascular endothelial growth factor (anti-VEGF) therapies are not options, standard treatment would be 'optimised standard of care', which could include laser therapy as a maintenance treatment. The Committee was aware of the publication of guidelines from the Royal College of Ophthalmologists suggesting the use of fluocinolone for some people and understood that there are currently no standard treatments for people with chronic diabetic macular oedema after other therapies have failed.

- 2.4 The Committee discussed the likely place of fluocinolone acetonide intravitreal implant in clinical practice. It heard from the clinical specialists that because fluocinolone acetonide intravitreal implant is a sustained-release low-dose long-acting steroid, it has clear advantages over other steroid implants, which are not licensed for the treatment of diabetic macular oedema. However, the Committee understood that there are significant side effects associated with the use of a steroid in the eye, especially the acceleration of cataract development and increased rates of raised intraocular pressure, and that these still occur with fluocinolone acetonide intravitreal implant. The Committee discussed whether the use of fluocinolone acetonide intravitreal implant in one eye could be associated with cataract development in the other eye. It understood from the manufacturer that it was not aware of any evidence suggesting this. Further, it heard that fluocinolone was not detectable in the blood. The Committee also heard from the clinical specialists that there is a spectrum of severity of diabetic macular oedema, and steroid treatment might be useful in those with more severe diabetic macular oedema if other treatments (including laser therapy) have failed and cataracts have already been removed. It understood that based on existing NICE guidance and clinical practice the patient population that would be considered for fluocinolone acetonide intravitreal implant would be those for whom laser photocoagulation and anti-VEGF therapies had failed.

Clinical effectiveness

- 2.5 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of fluocinolone acetonide intravitreal implant. The Committee noted that the main sources of evidence were the FAME A and B randomised controlled trials, which enrolled people with diabetic macular oedema and included a preplanned analysis defined by the median duration of diabetic macular oedema, which had been used to identify a subgroup of people with chronic diabetic macular oedema (that is, of more than 3 years' duration). It noted that in the FAME trials, patients were only treated in 1 eye and that the majority of patients were treated in their worse-seeing eye. The Committee noted that fluocinolone acetonide intravitreal implant was associated with statistically significant gains in the proportion of patients with chronic diabetic macular oedema who had a more than 15-letter increase in best corrected visual acuity (BCVA) from baseline compared with the sham injection group. It also noted that mean change in BCVA from baseline at month 36 of the FAME trials was statistically significantly greater in the fluocinolone acetonide intravitreal implant group compared with the sham injection group. The Committee concluded that fluocinolone acetonide intravitreal implant showed greater clinical effectiveness than sham injection in people with chronic diabetic macular oedema.
- 2.6 The Committee discussed the characteristics of the FAME trial population and how these related to the patient group specified in the marketing authorisation for fluocinolone acetonide intravitreal implant and to the group of patients likely to receive treatment in UK clinical practice. The Committee noted that the efficacy data submitted were based on a subgroup defined as having chronic disease with a duration of longer than 3 years, rather than as unresponsive to available therapies as specified in the marketing authorisation. The Committee further noted that some patients included received additional treatments during the trials such as laser photocoagulation and anti-VEGF injections. The Committee discussed the concerns that this implied that in the FAME trials fluocinolone acetonide intravitreal implant was not being used as specified in the marketing authorisation. The Committee noted the manufacturer's submission and comments on the appraisal consultation document stating that the patients in the FAME trials had poor visual acuity, and that the patients in the comparator arm had disease that was responding poorly to the background therapies when given in the trial. However, the Committee remained concerned that the data from

the FAME trials did not specifically reflect a group of patients who had disease that was insufficiently responsive to other therapies because people in the FAME trials did not necessarily have disease that was unresponsive to treatment with anti-VEGF or laser photocoagulation before randomisation. The Committee considered that this could affect the levels of response observed in clinical practice because one of the mechanisms of action of corticosteroids was to act on VEGF. It noted comments received on the appraisal consultation document that studies of other intravitreal corticosteroids (such as triamcinolone) have shown a beneficial effect on macular oedema when used after anti-VEGF treatments. The Committee remained concerned that the data from the trials may not be fully representative of the group of people who would be receiving fluocinolone acetonide intravitreal implant in UK clinical practice. However, it concluded that although there is uncertainty about the generalisability of the trial data to UK clinical practice, fluocinolone acetonide intravitreal implant is likely to be clinically effective in this population.

- 2.7 The Committee considered the manufacturer's approach to conducting an indirect comparison of fluocinolone acetonide intravitreal implant and laser photocoagulation using the FAME trials and the DRCR Protocol B study (2008). The Committee was aware of the Evidence Review Group's (ERG's) concerns over the value of the indirect comparison given the absence of a common comparator to link the FAME studies with the identified DRCR Protocol B study. It also noted that the retinopathy in patients included in the DRCR study was not as severe as in the FAME trials; that 40% of the DRCR population was laser-naive; and that in the DRCR study there was no stipulation on duration of diabetic macular oedema at randomisation. The Committee concluded that the indirect comparison could not be interpreted with confidence and in any case was inappropriate to the scope for this appraisal, which considered fluocinolone acetonide intravitreal implant when diabetic macular oedema has been insufficiently responsive to available therapies.
- 2.8 The Committee considered the evidence for adverse events associated with fluocinolone acetonide intravitreal implant. It was aware that fluocinolone acetonide intravitreal implant was associated with the formation or progression of cataract. It noted that although there were similar rates of pre-existing cataract between the 2 trial groups (77.9% and 77.0%) among people who were phakic (still had their natural lens) at baseline, cataract surgery was needed by a greater

percentage (85.1% versus 36.4%) of these people in the fluocinolone acetonide intravitreal implant group than in the sham injection group. The Committee heard from clinical specialists that the majority of people with chronic diabetic macular oedema would be likely to develop cataracts at some stage but that fluocinolone acetonide intravitreal implant might accelerate this. The Committee also noted that administration of fluocinolone acetonide intravitreal implant was associated with increased intraocular pressure: 5.3% of people in the fluocinolone group needed intraocular pressure-lowering surgery compared with 0% in the sham injection group. The Committee heard from clinical specialists that intraocular pressure-lowering surgery was a particular concern and for this reason, in addition to the associated acceleration of cataract development, clinicians would be likely to use fluocinolone acetonide intravitreal implant conservatively and be reluctant to use it too early in the treatment pathway. The Committee concluded that it was appropriate to take account of these adverse events when considering the approach to economic modelling.

Cost effectiveness

- 2.9 The Committee considered the manufacturer's economic model and sensitivity analyses, and discussed the key parameters used in it. The Committee noted the sensitivity of the model to the assumptions about the relationship between a person's treated eye and their overall visual acuity, the number of fluocinolone acetonide intravitreal implant treatments in the first 3 years, assumptions about the benefits of treatment after month 36, the rate of re-treatment, and the source of health-related quality of life values. The Committee concluded that the cost-effectiveness estimates were most sensitive to the source of health-related quality of life values, the assumption that a person's overall visual acuity related only to their treated eye, and the assumption that all treated eyes were better-seeing eyes.
- 2.10 The Committee considered the ERG's critique of the manufacturer's original base-case results. It was aware that the ERG had made a series of explorations using the manufacturer's original base-case incremental cost-effectiveness ratio (ICER) of £22,600 per quality-adjusted life year (QALY) gained as a starting point. The Committee noted that by correcting an error relating to the application of annual discontinuation rates in the model, and by changing the formulae for

averaging male and female mortality rates and for calculating the percentage of patients remaining on fluocinolone acetonide intravitreal implant beyond 9 years, the ERG's revisions increased the manufacturer's original base-case ICER from £22,700 to £26,500 per QALY gained for fluocinolone acetonide intravitreal implant compared with optimised standard of care without the patient access scheme. The Committee agreed that the ERG's initial error corrections to the model were appropriate.

2.11 The Committee went on to consider the ERG's further explorations to the original model, which were included in the manufacturer's revised model submitted for the rapid review:

- aligning assumptions about the rate of laser administrations per patient in the optimised standard of care group for year 1 of the model with the trial data
- applying revised unit costs for some adverse events
- revising the assumptions about the extrapolation of benefits beyond 3 years in the model
- applying an adjusted bilateral treatment rate in the fluocinolone acetonide intravitreal implant group of 85.2% of the treatment rate in the optimised standard of care group
- use of a 10-letters response criterion
- applying the absolute cost and quality of life uplift associated with bilateral treatment in the optimised standard of care group to the patients in the fluocinolone group needing bilateral treatment but for whom it was contraindicated
- applying the cost of blindness when only the treated eye fell below a BCVA of 35 letters rather than both eyes.

The Committee concluded that the above amendments to the assumptions in the economic model submitted by the manufacturer for the rapid review were reasonable.

2.12 The Committee discussed the assumption in the model that 20% of patients were treated in their best-seeing eye, 40% in their worse-seeing eye and 40% of

patients were treated in both eyes. The Committee noted the manufacturer's comment on the appraisal consultation document that in the FAME trials the majority of the patients had their worse-seeing eye treated because of ethical considerations but that in clinical practice, more patients would be treated in their best-seeing eye because this is more likely to protect functional vision. The Committee agreed that this could be the case but considered that currently there is a lack of evidence. It concluded that the assumption of 20% of the patients being treated in their best-seeing eye, 40% in their worse-seeing eye and 40% of patients receiving bilateral treatment was reasonable.

- 2.13 The Committee discussed the use of second and subsequent fluocinolone acetonide intravitreal implants and the assumption in the model of re-treatment only after 36 months. It noted that the summary of product characteristics states that an additional implant may be administered after 12 months if the patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening diabetic macular oedema. The Committee heard from the manufacturer that this wording was included in the summary of product characteristics because patients in the FAME trials could receive a further implant after 12 months. However, subsequent research showed that the effect of the corticosteroid should last 36 months. The Committee understood from the manufacturer that it does not promote having the implants more frequently than once every 36 months and that there are currently no data available demonstrating further benefit from reimplantation. The Committee accepted the assumption in the model of no more than 1 implant every 36 months.
- 2.14 The Committee discussed the fact that the model did not apply quality of life detriments to adverse events such as cataracts, glaucoma or raised intraocular pressure. The Committee noted the manufacturer's rationale that the impact of adverse events such as cataract formation on visual acuity was incorporated in the overall utility measures, that the application of these decrements would be short in duration and therefore have a minimal impact on the ICERs, and that the decrements associated with surgery would depend on when a patient chose to have surgery. Nevertheless, the Committee concluded that if disutilities associated with operations, procedures and hospital attendances (such as cataract removal, glaucoma surgery, retinal detachment surgery, vitrectomy and treatment of endophthalmitis) had been taken into account the ICERs would increase.

- 2.15 The Committee discussed the utility values for the better-seeing eye used in the economic model. The Committee noted that the manufacturer's original analyses had been based on Brown et al. (2000) utilities. It further noted that the ERG's explorations of the manufacturer's original model retained the Brown et al. (2000) utility values, and also explored the effect of applying utility values from Brown et al. (1999) and from a regression analysis in the manufacturer's submission for NICE technology appraisal guidance 237 on ranibizumab for the treatment of diabetic macular oedema (replaced by [technology appraisal guidance 274 on ranibizumab for treating diabetic macular oedema](#)). The Committee agreed that the utility values may vary in their appropriateness in being applied to people with chronic diabetic macular oedema. It accepted that the utility values from the manufacturer's submission for NICE technology appraisal guidance 237 were relatively insensitive to changes in visual acuity and therefore ICERs using these utilities may be numerically too high.
- 2.16 The Committee discussed further the relative merits of Brown et al. (1999) and Brown et al. (2000). It was aware that the Brown et al. (1999) utility values were based on a larger population with a mix of eye diseases whereas the Brown et al. (2000) study was based on a smaller population with age-related macular oedema (but not diabetic macular oedema). It noted that the data from Brown et al. (2000) included a large drop in utility values between some health states, which may have arisen from the smaller patient numbers in each health state. It also noted that utility values from Brown et al. (2000) for the best health states were higher than would be expected for people with chronic diabetic macular oedema, who are usually older people with comorbidities and this, in turn, increased the uncertainty around the validity of this source of utility values. The Committee heard from the ERG that Brown et al. (2002) found no difference in the reduction in the quality of life associated with similar levels of visual acuity loss depending on the causes of vision impairment. The Committee considered the manufacturer's rationale for using Brown et al. (2000) values based on the higher proportion of patients with oedema compared with Brown et al. (1999). It also noted that the manufacturer restated in its comment on the appraisal consultation document that Brown et al. (2000) represents a more accurate source of utility values for people with diabetic macular oedema. However, the Committee was not persuaded that this outweighed the benefits of the larger sample size and the associated finer delineation of utilities possible with larger patient numbers. The Committee concluded that there were limitations to using

the available utility values to model the health-related quality of life of the group of people with chronic diabetic macular oedema. However, of the available source of utility values, Brown et al. (1999) had advantages because of the size of the sample included in the study. Because there were some uncertainties about the most appropriate source of utility values for this patient population the Committee agreed to consider a range of ICERs based on both Brown et al. (1999) and Brown et al. (2000).

- 2.17 The Committee noted that the manufacturer had also included analyses using utility values from Czoski-Murray et al. (2009) and Heintz et al. (2012). The Committee discussed the appropriateness of using the values from Heintz et al. (2012) and considered that the very slight differences between utilities for the loss of better-seeing eye vision relative to worse-seeing eye vision lacked face validity. The Committee then discussed the utility values presented in Czoski-Murray (2009). It understood that the source of utility values had been considered for the appraisal of ranibizumab for the treatment of diabetic macular oedema (NICE technology appraisal guidance 237, replaced by [NICE's technology appraisal guidance 274 on ranibizumab for treating diabetic macular oedema](#)) and noted that using these utility values resulted in ICERs in between the ones obtained using Brown et al. (1999) and Brown et al. (2000). The Committee agreed to consider Czoski-Murray et al. (2009) as another source of utility values for this appraisal.
- 2.18 The Committee discussed the most appropriate adjustments needed to the better-seeing eye utility values in the model when the worse-seeing eye or both eyes were treated. The Committee considered the 6 scenario analyses carried out by the ERG (see [section 1.38](#)) which varied the health-related quality of life impact of changes in the vision of the worse-seeing eye and the resultant QALY gain associated with treatment of the worse-seeing eye or both eyes. The Committee understood the concerns of the ERG about using the Heintz et al. (2012) data to calculate the amount of gain from treating the worse-seeing eye, because of the small numbers of patients in some of the visual acuity levels and also because the manufacturer's calculation did not account for visual acuity in the better-seeing eye being correlated with visual acuity in the worse-seeing eye. The Committee also discussed the utilities for worse-seeing eyes in Brown et al. (1999) and heard from the ERG about an additional study, Sahel et al. (2007), which also showed that the visual acuity in the worse-seeing eye has little impact

on health-related quality of life unless it is severely affected. The Committee was aware that there could be psychological benefits from treating the worse-seeing eye that had not been captured in the calculation of the QALY. However, the Committee noted that the FAME trials collected data (with a majority of worse-seeing eyes) on the effect of visual impairment on quality of life using the disease-specific VFQ-25 questionnaire, and that this had shown no difference between the groups treated with fluocinolone acetonide intravitreal implant and those treated with sham injection. On balance, the Committee considered scenario analysis 3 (which assumed that changes in vision for people treated in their worse-seeing eye had 30% of the health-related quality of life impact of the same change in vision from treating their better-seeing eye) to be the most appropriate for decision-making. The Committee was not persuaded that 30% was an unreasonable reflection of the clinical situation for people with chronic diabetic macular oedema and noted that this was also consistent with previous appraisals.

- 2.19 The Committee then considered the cost-effectiveness results based on data from the FAME trials for all patients with chronic diabetic macular oedema taking into account its concerns (sections 2.9 to 2.18). The Committee noted that the most plausible ICER for fluocinolone acetonide intravitreal implant compared with optimised standard of care in the original guidance was at least £47,600 using the utilities from Brown et al. (2000) and £80,000 using the utilities from Brown et al. (1999) per QALY gained. The Committee noted that with the patient access scheme the ICERs were reduced to £37,600 using the utilities from Brown et al. (2000), £42,700 using the utilities from Czoski-Murray et al. (2009) and £63,500 using the utilities from Brown et al. (1999) per QALY gained. The Committee considered that the lowest of these estimates remained over £30,000 per QALY gained and therefore outside the range normally considered cost effective (£20,000 to £30,000 per QALY gained). It also noted that there was substantial uncertainty in these estimates, particularly in the extent to which the results of the clinical trial data included in the analyses could be applied to the population of people who would receive treatment in clinical practice. The Committee concluded that fluocinolone acetonide intravitreal implant could not be recommended as a cost-effective use of NHS resources for treating people with chronic diabetic macular oedema that is insufficiently responsive to available therapies.

- 2.20 The Committee discussed the subgroup of people with chronic diabetic macular oedema who had treatment in an eye with a pseudophakic lens. The Committee acknowledged that this is an identifiable subgroup of people with chronic diabetic macular oedema. The Committee noted that the numbers of patients in the subgroup were approximately half the chronic diabetic macular oedema population in the FAME trials and that the clinical effectiveness in terms of 15-letter gain in visual acuity in this subgroup was numerically worse than that in the total population (albeit with wide confidence intervals). The Committee considered that the comparatively small numbers of such patients in the FAME trials led to uncertainty in the estimates of clinical effectiveness for this group and thus in the estimates from the economic modelling but accepted that the subgroup proposed was reasonable. The Committee also considered that its concerns about the extent to which the data for the subgroup were representative of the group of people who would receive fluocinolone acetonide intravitreal implants in UK clinical practice remained valid (section 2.6). However, on balance, the Committee concluded that fluocinolone acetonide intravitreal implant had been shown to be clinically effective in this subgroup of people.
- 2.21 The Committee considered the cost effectiveness of fluocinolone acetonide intravitreal implant in the pseudophakic subgroup. It noted that the most plausible ICER for this subgroup in NICE's technology appraisal guidance on fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy was between £29,700 per QALY gained using the utilities from Brown et al. (2000) and £50,600 using the utilities from Brown et al. (1999). The Committee noted that with the patient access scheme, the ICERs presented by the ERG were £30,000 per QALY gained using the utilities from Brown et al. (1999), £21,000 per QALY gained using the utilities from Czoski-Murray et al. (2009) and £17,500 per QALY gained using the utilities from Brown et al. (2000). The Committee considered that the most plausible estimates of cost effectiveness would be in the upper end of this range, and that there was significant uncertainty around this estimate. The Committee was persuaded that the technology had been shown to meet a clinical need in people whose disease is unresponsive to available therapies. On balance, the Committee concluded that fluocinolone acetonide intravitreal implant could be a cost-effective use of NHS resources and recommended it as an option for people with chronic diabetic macular oedema that is insufficiently responsive to available therapies and if the implant is to be used in an eye with an intraocular

(pseudophakic) lens.

Summary of Appraisal Committee's key conclusions

Key conclusion (sections 2.19, 2.21)

Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema 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 intravitreal implant with the discount agreed in the patient access scheme.

The Committee considered that the lowest of ICERs with the patient access scheme for people with chronic diabetic macular oedema remained over £30,000 per QALY gained and therefore outside the range normally considered cost-effective (£20,000 to £30,000 per QALY gained). The Committee concluded that fluocinolone acetonide intravitreal implant was not recommended as a cost-effective use of NHS resources for treating people with chronic diabetic macular oedema that is insufficiently responsive to available therapies.

The Committee noted that for the pseudophakic subgroup, the ICERs with the patient access scheme checked by the ERG were between £30,000 per QALY gained using the utilities from Brown et al. (1999) and £17,500 per QALY gained with the utilities from Brown et al. (2000). It was persuaded that the technology had been shown to meet a clinical need in people whose disease is unresponsive to available therapies. The Committee concluded that fluocinolone acetonide intravitreal implant was a cost-effective use of NHS resources.

Current practice

Clinical need of patients, including the availability of alternative treatments (sections 2.2, 2.3)

The Committee was aware of comments from patient experts describing the significant negative impact that visual impairment has on the physical and emotional wellbeing of people with diabetic macular oedema.

The Committee was aware that NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema is the only NICE guidance relating specifically to treating diabetic macular oedema and that it does not cover the treatment of people with unresponsive disease. The Committee understood that there are currently no standard treatments for people with chronic diabetic macular oedema after other therapies have failed.

The technology

Proposed benefits of the technology; how innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? (section 2.4)

The Committee heard from the clinical specialists that because fluocinolone acetonide intravitreal implant is a sustained-release low-dose long-acting steroid, it has clear advantages over other steroid implants, which the Committee was aware are not licensed for the treatment of diabetic macular oedema.

What is the position of the treatment in the pathway of care for the condition? (sections 2.3, 2.4)

The Committee noted that the marketing authorisation for fluocinolone acetonide intravitreal implant specified its use only when diabetic macular oedema was insufficiently responsive to available therapies and that this population was not covered by NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema. It understood that based on existing NICE guidance and clinical practice the patient population that would be considered for fluocinolone acetonide intravitreal implant would be those for whom laser photocoagulation and anti-VEGF therapies had failed.

Adverse reactions (section 2.8)

The Committee noted that the significant side effects associated with the use of a steroid in the eye, especially the acceleration of cataract development and increased rates of raised intraocular pressure, still occur with fluocinolone acetonide intravitreal implant.

Evidence for clinical effectiveness

Availability, nature and quality of evidence (sections 2.5, 2.7)

The Committee noted that the main sources of evidence were the FAME A and B randomised controlled trials.

The Committee noted the DRCR Protocol B study used by the manufacturer in its indirect comparison. The Committee was aware of the ERG's concerns about the indirect comparison and concluded that it could not be interpreted with confidence and was inappropriate to the scope of this appraisal.

Relevance to general clinical practice in the NHS (section 2.6)

The Committee noted that the efficacy data submitted were based on a subgroup defined as having chronic disease with a duration of longer than 3 years, rather than as unresponsive to available therapies as specified in the marketing authorisation. The Committee further noted that some patients included in the trials received additional treatments during the trial such as laser photocoagulation and anti-VEGF injections, and that this implied that in the FAME trials fluocinolone acetonide intravitreal implant was not being used as specified in the marketing authorisation. However, it concluded that although there is uncertainty about the generalisability of the trial data to UK clinical practice, fluocinolone acetonide intravitreal implant is likely to be clinically effective in this population.

Uncertainties generated by the evidence (section 2.6)

The Committee was concerned that the data from the FAME trials did not reflect a group of patients who had disease that was insufficiently responsive to other therapies because people in the FAME trials did not necessarily have disease that was unresponsive to treatment with anti-VEGF or laser photocoagulation before randomisation.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? (section 2.20)

The Committee discussed the subgroup of people with chronic diabetic macular oedema who had treatment in an eye with a pseudophakic lens. The Committee considered that the comparatively small numbers of such patients in the FAME trials led to uncertainty in

the estimates of clinical effectiveness for this group and thus in the estimates from the economic modelling but accepted that the subgroup proposed was reasonable.

Estimate of the size of the clinical effectiveness including strength of supporting evidence (sections 2.5, 2.20)

The Committee concluded that fluocinolone acetonide intravitreal implant showed greater clinical effectiveness than sham injection in people with chronic diabetic macular oedema.

The Committee concluded that fluocinolone acetonide intravitreal implant had been shown to be clinically effective in the subgroup of people who had a pseudophakic lens.

Evidence for cost effectiveness

Availability and nature of evidence (sections 2.9, 2.10)

The Committee considered the manufacturer's model and the ERG's critique submitted for the rapid review.

Uncertainties around and plausibility of assumptions and inputs in the economic model (sections 2.14, 2.16, 2.20)

The Committee concluded that the manufacturer's model did not take into account the disutilities associated with operations, procedures and hospital attendances which if taken into account would cause the ICER to be even higher.

The Committee concluded that there were limitations to using the available utilities to model the health-related quality of life of the group of people with chronic diabetic macular oedema.

The Committee considered that the comparatively small numbers of patients who had a pseudophakic lens in the FAME trials led to uncertainty in the estimates of clinical effectiveness for this group and thus in the estimates from the economic modelling.

Incorporation of health-related quality-of-life benefits and utility values; have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they

been considered? (sections 2.16, 2.17)

The Committee concluded that there were limitations to using the available utilities to model the health-related quality of life of the group of people with chronic diabetic macular oedema and agreed to consider a range of ICERs based on both Brown et al. (1999) and Brown et al. (2000).

The Committee noted that the manufacturer had also included analyses using utility values from Czoski-Murray et al. (2009) and Heintz et al. (2012). The Committee discussed the appropriateness of using the values from Heintz et al. (2012) and considered that the very slight differences between utilities for the loss of better-seeing eye vision relative to worse-seeing eye vision lacked face validity. It understood that the utility values from Czoski-Murray et al. (2009) had been considered for the appraisal of ranibizumab for the treatment of diabetic macular oedema and agreed to consider it as another source of utility values for this appraisal.

Are there specific groups of people for whom the technology is particularly cost effective? (section 2.21)

The Committee discussed the subgroup of people with chronic diabetic macular oedema who had treatment in an eye with a pseudophakic lens and concluded that it was a cost-effective use of NHS resources.

What are the key drivers of cost effectiveness? (section 2.9)

The Committee concluded that the cost-effectiveness estimates were most sensitive to the source of health-related quality of life values and the assumption that a person's overall visual acuity related only to their treated eye.

Most likely cost-effectiveness estimate (given as an ICER; sections 2.19, 2.21)

The Committee noted that for all patients with chronic diabetic macular oedema, with the patient access scheme, the ICERs were £37,600 using the utilities from Brown et al. (2000), £42,700 using the utilities from Czoski-Murray et al. (2009) and £63,500 using the utilities from Brown et al. (1999) per QALY gained.

The Committee noted that for the pseudophakic subgroup, the ICERs with the patient access scheme presented by the ERG were £30,000 per QALY gained using the utilities

from Brown et al. (1999), £21,000 per QALY gained with the utilities from Czoski-Murray et al. (2009) and £17,500 per QALY gained with the utilities from Brown et al. (2000).

Additional factors taken into account

Patient access schemes (PPRS)

The manufacturer of fluocinolone acetonide intravitreal implant has agreed a patient access scheme with the Department of Health in which fluocinolone acetonide intravitreal implant will be available with a discount. The details of the scheme were provided as commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

End-of-life considerations

Not applicable.

Equalities considerations and social value judgements

The Committee concluded there were no issues relating to the equalities legislation, and there was no need to alter or add to its recommendations.

3 Recommendations for further research

- 3.1 Further research is recommended to resolve uncertainties about the cost effectiveness of fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema. This should focus on a group of patients whose condition is unresponsive to other available therapies, and include measures of efficacy and health-related quality of life. Research should focus on identifying appropriate utility values, taking into account the utility values for different levels of visual acuity and the relative relationship in utility values from treating the best-seeing and the worse-seeing eye. The appropriateness of generalising utility values from one group of eye conditions to another group would also be of value.

4 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy (NICE technology appraisal 271) was prepared by Warwick Evidence:

- Cummins E, Shyangdan D, Royle P, Johnston R, Ho V, Briscoe S, Lois N, Waugh N. Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema: A Single Technology Appraisal. Warwick Evidence, 2012

The critique for this appraisal was prepared by Warwick Evidence:

- Cummins E, Lois N. Waugh N. Fluocinolone for diabetic macular oedema: evidence review group report on Alimera submission for rapid review of TA 271.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in 1 were also invited to make written submissions. Organisations listed in 2 and 3 had the opportunity to give their expert views. Organisations listed in 1, 2 and 3 also have the opportunity to appeal against the final appraisal determination.

1. Manufacturer/sponsor:

- Alimera Sciences Inc

2. Professional/specialist and patient/carer groups:

- Diabetes UK
- Fight for Sight
- Organisation of Blind African Caribbeans
- Royal National Institute of Blind People (RNIB)
- Royal College of Nursing

- Royal College of Ophthalmologists
- Royal College of Physicians

3. Other consultees:

- Department of Health
- Welsh Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Novartis Pharmaceuticals
- Pfizer
- Roche Products

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Clare Bailey, Consultant Ophthalmologist, nominated by Alimera Sciences Inc – clinical specialist
- Professor Yit Yang, Consultant Ophthalmologist, Nominated by Royal College of Ophthalmologists – clinical specialist
- Clara Eaglen, Policy and Campaigns manager, nominated by Royal National Institute of Blind People – patient expert.

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific

issues and comment on factual accuracy.

- Alimera Sciences Inc.