

# Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy

Technology appraisal guidance

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[www.nice.org.uk/guidance/ta613](http://www.nice.org.uk/guidance/ta613)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance partially replaces TA301.

# 1 Recommendations

- 1.1 Fluocinolone acetonide intravitreal implant is not recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye).
- 1.2 This recommendation is not intended to affect treatment with fluocinolone acetonide intravitreal implant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

## Why the committee made these recommendations

Treatments for untreated chronic diabetic macular oedema include laser therapy and anti-vascular endothelial growth factors (VEGFs). There are no further treatment options for eyes with a natural lens (phakic eyes).

The company submitted evidence for people with phakic eyes and symptomatic cataracts. Clinical trial evidence compares the effectiveness of fluocinolone acetonide intravitreal implant and sham in people with chronic diabetic macular oedema who already had at least 1 laser treatment. Only very few people had anti-VEGFs before the trial and few people had phakic eyes with symptomatic cataracts. Also, non-comparative studies used to support the company's submission only include few people with phakic eyes and symptomatic cataract. No other data for this group have been identified. This makes it difficult to establish if fluocinolone acetonide intravitreal implant works better than usual care for these people, especially in the long term.

Because of the lack of clinical evidence, the cost-effectiveness estimates for fluocinolone acetonide intravitreal implant are also uncertain. Even the lowest clinically plausible cost-effectiveness estimates are substantially higher than what NICE normally considers an acceptable use of NHS resources. Therefore, fluocinolone acetonide intravitreal implant is not recommended for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye).

## 2 Information about fluocinolone acetonide intravitreal implant

### Information about fluocinolone acetonide intravitreal implant

<b>Marketing authorisation indication</b>	Fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences) is indicated for 'the treatment of vision impairment associated with chronic diabetic macular oedema, (DMO) considered insufficiently responsive to available therapies'.
<b>Dosage in the marketing authorisation</b>	Fluocinolone acetonide intravitreal implant is administered through intravitreal injection. Each implant contains 0.19 mg of fluocinolone acetonide and releases fluocinolone acetonide for up to 36 months.
<b>Price</b>	£5,500 per implant (excluding VAT, BNF online, accessed June 2019). The company has a commercial arrangement. This makes fluocinolone acetonide intravitreal implant available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence.

## 3 Committee discussion

The appraisal committee ([section 4](#)) considered evidence submitted by Alimera Sciences and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

### Company's positioning in treatment pathway

#### The company's proposed population is narrower than that in the NICE scope and the marketing authorisation

3.1 [NICE's technology appraisal guidance on fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy](#) recommends fluocinolone acetonide intravitreal implant only for eyes with an intraocular (pseudophakic) lens. In this part review, the committee considered the effectiveness of fluocinolone acetonide intravitreal implant compared with usual care in phakic eyes. The company submitted evidence for people with phakic eyes and symptomatic cataract, a population identified in [NICE's guideline on the management of cataracts in adults](#). The committee understood that these people should be offered cataract surgery but that waiting time for cataract surgery can vary. Also, it agreed that the company's proposed population is narrower than the NICE scope and the marketing authorisation for fluocinolone acetonide intravitreal implant. The committee concluded that it is appropriate to appraise the cost effectiveness of fluocinolone acetonide intravitreal implant in phakic eyes with symptomatic cataracts compared with usual care.

### Potential new treatment option

#### People with diabetic macular oedema in phakic eyes would welcome a new treatment option

3.2 Diabetic macular oedema is a common complication associated with diabetic retinopathy that can lead to loss of vision. Complications of diabetic macular oedema include cataracts and glaucoma. The patient experts explained that diabetic macular oedema can have a substantial impact on patients' and carers' quality of life. Patients and carers can experience anxiety and stress because of

the chronic nature of the disease and potential sight loss. Clinical and patient experts highlighted that people with diabetic macular oedema that does not respond well enough to available therapies and who have a natural lens currently have to wait until after cataract surgery before they are offered intravitreal steroid implants. The committee recalled that waiting times for cataract surgery can vary. It was aware that, based on the recommendations in [NICE's technology appraisal guidance on fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy](#), it is increasingly common for people to get cataract surgery followed immediately by fluocinolone acetonide intravitreal implant during the same procedure. Therefore, if cataract surgery waiting times were improved, the wait for fluocinolone acetonide intravitreal implant for people within the company's proposed population may also be reduced. However, the committee noted that this could not be addressed in a technology appraisal. Clinical experts confirmed that, in some cases, people continue to have anti-vascular endothelial growth factors (anti-VEGFs), even if they do not work well. The clinical and patient experts explained that adverse events, such as cataract and increased intraocular pressure, caused by the fluocinolone acetonide intravitreal implant are manageable. The committee concluded that people with diabetic macular oedema in phakic eyes would welcome a new treatment option.

## Clinical management

### Both laser treatment and anti-VEGFs are appropriate comparators for decision making

- 3.3 The clinical expert explained that NHS clinical practice for treating diabetic macular oedema has changed since anti-VEGFs were introduced. The committee was aware that most people will initially have anti-VEGFs and that in phakic eyes they might be continued even if they do not work well. The committee understood that there is no difference between people offered laser therapy and anti-VEGFs and that treatment choice is often guided by clinical judgement. It therefore concluded that both laser treatment and anti-VEGFs are appropriate comparators for decision making.

## Clinical evidence

### The clinical trial does not reflect NHS clinical practice

3.4 The clinical evidence for fluocinolone acetonide intravitreal implant came from 2 phase 3 randomised sham-injection controlled trials that were analysed as 1 trial (FAME). The follow up was 36 months. FAME was carried out between 2007 and 2010 before anti-VEGFs were introduced. Most people in the trial had previously had at least 1 laser treatment while only few had had anti-VEGFs. Level of response to previous treatment was not an inclusion criterion of the trial. During the trial, people in both arms could have rescue treatments, such as laser therapy, anti-VEGFs and steroids. The company presented data on rescue therapy for 2 subgroups: people with non-chronic diabetic macular oedema and people with chronic diabetic macular oedema. In the latter group, rescue therapy was more common in the sham arm than the intervention arm; rescue laser therapy (62% compared with 41%), anti-VEGFs (15% compared with 3%) and triamcinolone (24% compared with 8%). The company did not present rescue therapy data for phakic eyes. The committee understood that most people with diabetic macular oedema will have anti-VEGFs and that rescue therapy is not used in clinical practice. Also, in FAME, very few people had symptomatic cataract at baseline but the company positions fluocinolone acetonide intravitreal implant for people with diabetic macular oedema in phakic eyes with symptomatic cataract. Therefore, the committee concluded that FAME does not reflect NHS clinical practice, and that results from FAME may not be generalisable to people with chronic diabetic macular oedema in phakic eyes with symptomatic cataract seen in the NHS.

### The clinical evidence for people with phakic eyes with symptomatic cataract is limited because of very small numbers

3.5 Visual acuity was the primary outcome in FAME. In people with chronic diabetic macular oedema, the mean change from baseline to month 36 in best corrected visual acuity (BCVA) score was an additional 7.6 letters in the intervention arm and an additional 1.8 letters in the sham arm ( $p=0.004$ ). The company explained that, in the treatment arm, the improvement was higher in the group with eyes that were phakic at baseline and became pseudophakic after cataract surgery during the study than in eyes that were pseudophakic at baseline (11 compared with 7 letters gained). However, this was not statistically significant. An



improvement was also seen in both arms in the people with phakic eyes and a clinical history of cataract although the improvement was not statistically significant. The data are confidential and cannot be reported here. The clinical expert confirmed that a 5-letter increase in BCVA is considered clinically meaningful. The committee understood that diabetic macular oedema is a disease of the retina and that phakic eyes might benefit from treatment in a similar way to pseudophakic eyes. The clinical expert also explained that treatment of diabetic macular oedema in phakic eyes might save the retina and possibly lead to better outcomes after cataract surgery. However, the committee noted that the FAME trial only included a very small number of people with a clinical history of cataract. There was no prespecified statistical analysis plan to do a subgroup analysis for people with phakic eyes with symptomatic cataract, the company's proposed population for this appraisal. The clinical expert explained that people with cataract are often excluded from clinical trials for diabetic macular oedema. Cataracts make it difficult to see the retina and to assess retinal thickness, which is a relevant clinical factor when assessing diabetic macular oedema. The committee acknowledged the difficulties of doing clinical trials in people with phakic eye and symptomatic cataract. However, it was concerned about the lack of clinical data for this population. The committee agreed that it is plausible that the fluocinolone acetonide intravitreal implant improves visual acuity compared with usual care in phakic eyes with symptomatic cataract, but that this is highly uncertain because the evidence from clinical trials was very limited. The committee concluded that there were not enough data to establish if fluocinolone acetonide intravitreal implant worked better than usual care in phakic eyes with symptomatic cataract.

## **Non-comparative evidence does not reduce uncertainty in the clinical outcomes because of the extremely small number of people included**

- 3.6 The company presented data from 2 European registry studies that were done after anti-VEGFs were introduced as a treatment option. These studies included few people with phakic eyes and symptomatic cataract who had fluocinolone acetonide intravitreal implant on the same day as cataract surgery. The ERG identified further registry studies, but the company explained that these were inappropriate because it was difficult to identify people with phakic eyes and symptomatic cataract in these studies. The committee acknowledged that, in

England, [NICE's technology appraisal guidance on fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy](#) limits the use of fluocinolone acetonide implant to pseudophakic eyes and therefore limits the availability of UK non-comparative data. The committee understood that there is limited non-comparative evidence for phakic eyes with symptomatic cataract, therefore it concluded that it is difficult to establish whether fluocinolone acetonide intravitreal implant works better than usual care in this group.

## The cost-effectiveness evidence

### The model structure is acceptable for decision making

- 3.7 The company presented a state-transition Markov model. In the model, people moved from health state to health state every 3 months and this was modelled using transition probability matrices informed by the FAME trial. The model simulated both eyes and combined them into bilateral health states. The committee concluded that the model structure was acceptable for decision making.

### The BCVA results from the model differ from the FAME results, increasing the uncertainty of what would happen in the long term or in phakic eyes with symptomatic cataracts

- 3.8 The company validated their model by comparing modelled BCVAs with those seen in FAME. Most model inputs came from the FAME trial with some from non-comparative studies and additional data sources. The committee noted that BCVAs from the model output and FAME trial results were very different, particularly for the sham arm of FAME. It agreed that the effectiveness data used for the usual care arm should be modelled in line with FAME results (see section 3.9). The committee noted that the model included transition probabilities derived from the full population of FAME and discussed the differences between the FAME trial population and the company's proposed population for this appraisal. The committee concluded that BCVA outcomes predicted by the model did not reflect the data seen from FAME. Further uncertainty is introduced when data are extrapolated beyond the FAME trial period of 36 months, to people who previously had anti-VEGFs and to people with phakic eyes with symptomatic cataract.

## The net effect between the treatment arm and the sham arm should be modelled

3.9 In FAME, people in both arms could have rescue treatments which might result in improved vision. The treatment effectiveness in the FAME treatment arm captured both the effect of rescue treatments and fluocinolone acetonide intravitreal implant treatment. The improvement seen in the sham arm might be partly because of rescue therapy and partly because of placebo effect. The company included the full treatment effectiveness in the FAME treatment arm in their model but assumed no change in BCVA in the usual care arm. The company explained that this approach is taken because the sham arm of FAME does not represent current NHS clinical practice and that there is no recovery seen in usual care. Because rescue therapy was used in both arms in FAME, the ERG suggested modelling the net effect between treatment and sham arm. This accounts for the effectiveness seen in the sham arm of FAME and was included in the ERG's base-case model. It substantially increased the incremental cost-effectiveness ratio (ICER). The committee agreed that the sham arm in FAME does not represent current NHS clinical practice. However, it noted that both arms included people who had rescue therapies, and agreed that the same issue applied to the treatment arm. In response to consultation, the company presented a schematic and graphs illustrating possible visual acuity outcomes with different treatments. The committee was aware that these graphs represented theoretical outcomes from the model and FAME that it had considered at the first committee meeting. The committee concluded that modelling the net effect was more appropriate than assuming no change in BCVA for the usual care arm, although the trial data and the model outputs in relation to the trial data remained highly uncertain (see [section 3.5](#), [section 3.6](#) and [section 3.8](#)).

## It is reasonable to assume that people will have more than 1 implant during the first 3 years

3.10 The clinical experts explained that, in line with the summary of product characteristics, an additional fluocinolone acetonide intravitreal implant may be administered after 12 months if worsening or recurrent diabetic macular oedema results in decreased vision or an increase in retinal thickness. In their model, the company assumed an average of 1.06 implants per person over the first 3 years in line with non-comparative data from the Medisoft study.

However, based on the clinical trial FAME data, the ERG estimated people with chronic diabetic macular oedema had an average of 1.3 implants over the first 3 years. Non-comparative data from the IRISS study suggested that this number is 1.13 implants over the first 3 years. The ERG included the number from the IRISS study in their base-case model. The clinical expert confirmed that some people are likely to have a second implant within the first 3 years. The committee concluded that it is reasonable to assume people may have more than 1 implant during the first 3 years and accepted the ERG's base-case model assumption but noted that this was not a key driver of the cost-effectiveness results.

## It is plausible to assume some additional gain from retreatment after 3 years

3.11 The company assumed that people who are retreated after 3 years will experience continued gain in BCVA and that this gain would be similar to the gain seen for the first implant in months 3 to 36. The ERG stated that retreatment with fluocinolone acetonide intravitreal implant at year 3 is more likely to maintain the first 3 years gain in BCVA. The clinical experts confirmed that a second implant might result in additional BCVA gains. The committee concluded that an additional gain in BCVA with a second implant after 3 years is plausible.

## About 42% of people with diabetic macular oedema in phakic eyes with symptomatic cataract might get a second implant after 3 years

3.12 Each fluocinolone acetonide intravitreal implant releases 0.2 micrograms per day over about 3 years. The clinical expert explained that people whose diabetic macular oedema responds to the implant might be offered a second implant after 3 years. The clinical expert explained that an increase of 5 letters BCVA or an improvement of retinal thickness by more than 10% is considered clinically relevant. The company estimated that about 36% of people with phakic eyes in the FAME treatment arm would have been retreated because they achieved an improvement in BCVA of 15 or more letters. In people with phakic eyes who had their cataract removed during the trial, this number was higher (42.3%). The committee concluded that about 42% of people with phakic eyes and symptomatic cataracts will be retreated and accepted the assumption in the

ERG's base-case model.

## The number of monitoring visits for anti-VEGFs should be in line with registry data

- 3.13 Anti-VEGFs are established therapy for treating phakic eyes with symptomatic cataract. Therefore, the company included bi-monthly monitoring visits during year 1 (6 visits), 5 visits in year 2, and 4 visits in years 3, 4, 5 and 6. Data from ICE-UK suggested that people having anti-VEGFs are monitored 4 times a year. The committee discussed the frequency of anti-VEGF injections and the need for monitoring. It agreed with the assumption in the ERG's base-case model of 8 monitoring visits in year 1 and 4 in each following year.

## It is uncertain if the treatment continues to have an effect on vision outcomes for a lifetime after treatment has stopped

- 3.14 In the model, the company assumed that treatment effect is maintained for a lifetime even after treatment has stopped. The committee noted from the summary of product characteristics that each fluocinolone acetonide intravitreal implant lasts about 3 years. The committee agreed that there might be a continued treatment effect after treatment has stopped but it was uncertain how long this would last. The ERG was unable to directly explore the effect of continued treatment in the model but explored this issue by adjusting the time horizon in scenario analyses. The committee concluded that it is implausible to assume the continued treatment effect would last for a lifetime.

## Health-related quality of life

### The company's preferred utility values are acceptable for decision making

- 3.15 The company collected quality-of-life data using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) during FAME. It mapped these data using a published mapping algorithm (Rentz et al. 2014) to estimate quality of life for FAME data. These quality-of-life values were then used to provide values for BCVA in the best seeing eye and the worst seeing eye. Values were weighted and smoothed to obtain final utility values. The ERG had some concerns around the health-related quality-of-life data. It noted that previous

NICE appraisals within ocular diseases used the experimental lenses study by Czoski-Murray et al. (2009). The ERG provided some scenario analyses exploring the impact of different utility estimates on the cost effectiveness. The committee agreed that a disease specific instrument might be more responsive to changes in people's BCVA than the generic EQ-5D (NICE's preferred utility instrument). The committee accepted that there are different options to capture health-related quality of life for people with diabetic macular oedema. It was aware that carers' health-related quality of life may also be affected, but that it had not been shown evidence to capture this. Overall, the committee concluded that the use of NEI-VFG-25 and mapping algorithm was acceptable.

## Cost-effectiveness results

### The ICERs are highly uncertain, and there is no single most plausible ICER, but all plausible ICERs exceed £30,000 per quality-adjusted life year (QALY) gained

3.16 The company's deterministic base case suggested that the ICER for the fluocinolone acetonide intravitreal implant compared with laser therapy and anti-VEGFs combined was £2,187 per QALY gained. The committee noted that the company had not submitted new evidence or updated cost-effectiveness analyses at consultation. All analyses included the confidential commercial arrangement discount for the fluocinolone acetonide intravitreal implant. The ERG suggested several changes to the company's base-case model:

- FAME sham treatment effect for usual care (see [section 3.9](#)).
- Year 3 retreatment maintains vision (see [section 3.11](#)).
- Number of implants is 1.13 in the first 3 years in line with the IRISS study (see [section 3.10](#)).
- Increase in the percentage of responders to fluocinolone acetonide intravitreal implant (see [section 3.12](#)).
- Adjustment of monitoring visits for anti-VEGFs (see [section 3.13](#)).

- Minor corrections to the model structure.

When considered individually, most changes only had a small effect on the ICER. Modelling the net effectiveness (see section 3.9) reduced the QALY gain substantially and had the largest effect on the ICER (ICER changed to £73,256 per QALY gained). Combining all preferred ERG changes increased the ICER to £461,000 per QALY gained. The ERG reproduced the analyses to include the confidential commercial arrangement discount for the comparators. The resulting ERG base-case ICER was substantially higher than £30,000 per QALY gained (the exact ICER is confidential and cannot be reported here). The committee accepted most of the changes the ERG made (see sections 3.9 to 3.13), including the minor structural changes.

The committee discussed the additional sensitivity analyses done by the ERG and agreed that all explorations were valid, and most were clinically plausible. The committee understood that, for the ERG base case, the QALY gain for fluocinolone acetonide intravitreal implant was small, meaning the ICER changed dramatically between different clinically plausible scenarios. All were substantially higher than £30,000 per QALY gained. The ERG reproduced the sensitivity analyses to include the confidential commercial arrangement discount for the comparators. The resulting ICERs were substantially higher than £30,000 per QALY gained (the exact ICERs are confidential and cannot be reported here).

The committee noted that it had considered all available evidence. The committee concluded that the cost-effectiveness estimates were very uncertain but the most plausible ICERs were all substantially over £30,000 per QALY gained. This was higher than the range normally considered a cost-effective use of NHS resources. Therefore, it did not recommend fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies if the implant is to be used in an eye with a natural lens (phakic eye).

## Innovation

### The benefits of the fluocinolone acetonide intravitreal implant are captured in the cost-effectiveness analysis

- 3.17 The company considered the fluocinolone acetonide intravitreal implant to be innovative. The clinical experts stated that the fluocinolone acetonide intravitreal implant would be a substantial change in treating diabetic macular oedema in phakic eyes with symptomatic cataract because the long-lasting

effect reduces the need for repeated treatment and reduces treatment and follow-up burden. The committee concluded that fluocinolone acetonide intravitreal implant might be beneficial for the people with phakic eyes and symptomatic cataract but that it had not been shown evidence of any additional benefits that were not captured in the measurement of QALYs.

## Equality

### There are no equality issues relevant to the recommendation

- 3.18 The committee noted 2 potential equality issues raised by clinical experts. People with phakic eyes and symptomatic cataract are currently disadvantaged because they cannot have fluocinolone acetonide intravitreal implant. Some of these people continue to have anti-VEGFs even though their diabetic macular oedema does not respond well enough. These people must wait for cataract surgery before they can have the fluocinolone acetonide intravitreal implant. It was also noted in a consultation comment that people with cataract are often older with multiple comorbidities. The committee concluded that its recommendations do not have a different effect on people protected by the equality legislation than on the wider population. It concluded that there are no equality issues relevant to the recommendation.



## 4 Appraisal committee members and NICE project team

### Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

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

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### NICE project team

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

**Verena Wolfram**

Technical lead

**Alexandra Filby**

Technical adviser

**Joanne Ekeledo and Louise Jafferally**

Project managers

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## Accreditation

