NICE National Institute for Health and Care Excellence

NICE guidance

Fluocinolone acetonide intravitreal implant for treating recurrent non-infectious uveitis

Technology appraisal guidance
Published: 31 July 2019

www.nice.org.uk/guidance/ta590

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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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1 Recommendations

1.1 Fluocinolone acetonide intravitreal implant is recommended, within its marketing authorisation, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. It is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Treatments for recurrent non-infectious uveitis affecting the posterior segment of the eye include systemic corticosteroids, immunosuppressants and dexamethasone implants. These treatments can be disruptive to daily life, needing frequent hospital visits.

The clinical trial results for the fluocinolone acetonide intravitreal implant compared with limited current practice are difficult to interpret and very uncertain. The trial didn't directly measure health-related quality of life and the number of recurrences reported may be overestimated.

The cost-effectiveness estimates are also uncertain. However, if all the most plausible assumptions had been included in the model, most of the cost-effectiveness estimates would be within the range that NICE normally considers a cost-effective use of NHS resources, so the fluocinolone acetonide implant is recommended.

2 Information about fluocinolone acetonide intravitreal implant

Information about fluocinolone acetonide intravitreal implant

Marketing authorisation indication	Fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences) is indicated for 'prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye'.
Dosage in the marketing authorisation	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.
Price	£5,500 per implant (excluding VAT, British national formulary online [accessed May 2019]). The company has a commercial arrangement. This makes fluocinolone acetonide intravitreal implant available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) 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.

New treatment option

People with recurrent non-infectious uveitis affecting the posterior segment of the eye will welcome a new treatment option

3.1 Patient experts described the anxiety associated with having uveitis because of potentially worsening sight, if they will be able to continue working and how it affects their relationships and independence. They explained that existing treatments for controlling recurrent non-infectious uveitis can be burdensome and disruptive to daily life for both patients and their carers, needing frequent hospital visits for administration and monitoring. The patient experts described how having a treatment that lasts for 3 years had substantially increased their quality of life. They highlighted that the fluocinolone acetonide implant could be particularly beneficial for people who cannot have systemic treatments. One of the patient experts described how the effects of the dexamethasone implant had lasted for much less than the 6 months they had been expecting. The clinical experts also highlighted that biologic treatments are not effective in 20% to 30% of people with recurrent non-infectious uveitis and there is a need for alternative treatment options. The committee concluded that people with recurrent non-infectious uveitis affecting the posterior segment of the eye would welcome an additional treatment option, particularly one with long-lasting benefits.

Clinical management

The dexamethasone implant is a relevant comparator

3.2 The clinical experts explained that non-infectious uveitis is treated differently depending on whether the disease is:

- active (that is, current inflammation in the eye) or inactive (that is, limited inflammation, usually because of treatment with corticosteroids or immunosuppressants)
- systemic (when disease is not only in the eye) or non-systemic (when disease is limited to the eye)
- unilateral (when 1 eye is affected) or bilateral (when both eyes are affected).

There may also be local variation in treatment. Non-infectious uveitis without systemic disease may first be treated with local corticosteroids, followed by systemic corticosteroids or a dexamethasone implant. Multiple repeated dexamethasone implants may be given. Bilateral disease or unilateral disease with active systemic disease may first be treated with systemic corticosteroids, followed by immunosuppressants or dexamethasone implants. Treatments may also be used in combination. TNF-alpha inhibitors such as adalimumab may be an option after immunosuppressants. The marketing authorisation for the fluocinolone acetonide implant is for recurrent disease, so the clinical experts explained that they would most likely offer it to people who had already had corticosteroids. They explained that if the disease responded well to a dexamethasone implant, they would consider using a fluocinolone acetonide implant instead of another dexamethasone implant. The committee agreed that in NHS clinical practice in England, it was likely that the fluocinolone acetonide implant would be used after corticosteroids, as an alternative to the dexamethasone implant. The committee concluded that the dexamethasone implant was a relevant comparator for the fluocinolone acetonide implant.

Clinical evidence

The clinical trial may not fully reflect NHS clinical practice in England

3.3 The evidence for the fluocinolone acetonide implant came from the PSV-FAI-001 trial. This was a multicentre, randomised, double-blind trial in patients with chronic non-infectious uveitis affecting the posterior segment of the eye. It compared the fluocinolone acetonide implant with a sham injection. Patients in both treatment groups could have 'limited current practice': this was the corticosteroids and immunosuppressants that they had been having before enrolling in the trial but tapered off within the first 3 months. Other than treatments that were being tapered off, patients could not have corticosteroids or immunosuppressants until their uveitis recurred. This meant that after 3 months and before recurrence, people in the control group had no treatment. Additionally, before recurrence in the trial, trial investigators were encouraged to use systemic treatment only after local treatment had failed. The committee agreed that this may not reflect clinical practice in the NHS in England because the clinical experts had said that systemic treatment may be given first for bilateral or systemic disease (see section 3.2). The committee concluded that treatment in the trial may not fully reflect NHS clinical practice in England.

Recurrence of uveitis

Rates of recurrence of uveitis in the trial are likely overestimated

3.4 The primary outcome in the PSV-FAI-001 trial was the proportion of patients who had a recurrence of uveitis in the study eye within 6 months of having study treatment. After 12 months, the recurrence rate was 37.9% in the fluocinolone acetonide implant group and 97.6% in the control group. However, the committee noted that recurrence was assumed for patients who had missing data for the required eye examinations, or who had local or systemic treatments that were prohibited as part of the trial. The trial did not record why these

treatments were given, but the committee considered that they may have been used to treat the other eye or for an underlying condition (rather than for recurrent uveitis in the study eye). So, it agreed that the recurrence rates reported in the trial were likely overestimated.

Visual acuity

The fluocinolone acetonide implant improves visual acuity

3.5 Visual acuity was a secondary outcome in the PSV-FAI-001 trial. After 12 months, mean best-corrected visual acuity (BCVA) in the control group had increased from 64.9 letters to 69.2 letters. In the fluocinolone acetonide implant group, mean BCVA increased from 66.9 letters to 72.8 letters. The clinical experts explained that a 5-letter increase in BCVA is clinically meaningful. They highlighted that most of the people in the control group had had a recurrence of uveitis by 12 months, so would have had other treatments, which could explain the increase in BCVA in this group. The committee concluded that the fluocinolone acetonide implant improves visual acuity compared with current practice. However, it noted that visual acuity was not directly included in the economic model.

Adverse effects

Adverse effects associated with the fluocinolone acetonide implant are manageable in clinical practice

3.6 Common adverse effects of the fluocinolone acetonide implant include cataract and increased intraocular pressure. One of the patient experts explained that although developing a cataract did affect their sight, which reduced their quality of life, the cataract surgery was relatively straightforward and there was no lasting effect on their quality of life. The clinical experts stated that there was unlikely to be a big difference in the adverse effects of the fluocinolone acetonide implant compared with those of the dexamethasone implant. The committee noted that there were more older people in the control group of the trial, which may

have affected the rate of adverse effects compared with that in the fluocinolone acetonide implant group. But overall, the committee considered that the fluocinolone acetonide implant is well tolerated compared with other treatments for uveitis and that the adverse effects are manageable in clinical practice.

The company's economic model

A model that considers both eyes would have been preferred

3.7 The company presented a Markov model with 5 health states: on treatment, subsequent therapy, remission, permanent blindness and death. The model compared the fluocinolone acetonide implant with the treatments received in the control group in the PSV-FAI-001 trial (described as 'limited current practice', see section 3.3) in the study eye only. Treatment effectiveness was modelled using time to first uveitis recurrence in the study eye from the trial. The ERG highlighted that in a potentially bilateral disease, modelling should consider both eyes to fully capture the effect of sight loss on health-related quality of life, survival and costs. The clinical experts suggested that a large proportion of people with recurrent non-infectious uveitis have bilateral disease. In the trial, 67.8% in the fluocinolone acetonide implant group and 73.8% in the control group had bilateral disease at baseline. The company stated that it could not include both eyes in the full cost-effectiveness modelling because of a lack of data. The committee concluded that it would have preferred to have seen a model that took both eyes into account.

The model should include the possibility of multiple implants

3.8 The company's model assumed that each patient had only 1 fluocinolone acetonide implant. However, the clinical experts stated that they would consider using another fluocinolone acetonide implant after 3 years, if the disease had responded well to the first implant. The committee concluded that the model should include an option for retreatment with multiple fluocinolone acetonide implants (see section 3.13).

The ERG's model using the dexamethasone implant as a

comparator is preferred

3.9 Based on the clinical experts' description of the treatment pathway, the committee considered that the dexamethasone implant was a relevant comparator for the fluocinolone acetonide implant (see section 3.2). The ERG did a naive analysis, estimating the potential effectiveness of the dexamethasone implant compared with limited current practice (based on evidence used to inform NICE technology appraisal guidance on adalimumab and dexamethasone for treating non-infectious uveitis) so that it could include the dexamethasone implant in the model as a comparator. The analysis assumed that the dexamethasone implant was more effective than limited current practice, with a hazard ratio for time to first recurrence of 0.456. The ERG also presented scenario analyses that assumed the effectiveness of the dexamethasone implant was equal to that of the fluocinolone acetonide implant. The clinical experts suggested that they expected the effectiveness of the fluocinolone acetonide implant to be similar to that of the dexamethasone implant, for the time that the treatments remain active. The committee noted that the benefit of the dexamethasone implant lasted for almost 6 months in the model, whereas patient experts had experience of the implant lasting less than 6 months (see section 3.1). The patient experts explained that repeated dexamethasone implants can only be given after vision has deteriorated, which means a patient may have several weeks of reduced vision between implants. The committee considered that while the treatments remain active, both the fluocinolone acetonide and dexamethasone implants are likely to have a similar effect on visual acuity. However, on average over 3 years (with repeated dexamethasone implants) the fluocinolone acetonide implant may be more effective in preventing recurrence of uveitis. In response to the appraisal consultation document, the company presented its own naive analysis comparing the fluocinolone acetonide implant with the dexamethasone implant. The company scaled down the time to recurrence curve for the fluocinolone acetonide implant from 3 years to 6 months, to model the efficacy of the dexamethasone implant. The ERG highlighted that using this method made the recurrence rate in the dexamethasone implant group higher than in the fluocinolone acetonide implant group. The committee agreed that the company's method of estimating the comparative effectiveness of the dexamethasone implant was

implausible. In the company's updated analyses, patients could have another implant if treatment failed, rather than waiting until the end of the expected duration of the implants (6 months for the dexamethasone implant or 3 years for the fluocinolone acetonide implant). In the company's analyses, the maximum number of dexamethasone implants that someone could have was 3, which the company explained was because of constraints of the way the new analysis was implemented in the model. The committee noted that this led to more time on treatment in the fluocinolone acetonide implant group, because it could last for up to 3 years. The committee noted that in the ERG's original analysis, patients could have 6 dexamethasone implants in 3 years, which it agreed was a better comparison because the time on treatment was the same for both groups. The committee understood that both the company's and the ERG's methods of comparing the fluocinolone acetonide implant with the dexamethasone implant were based on assumptions but concluded that the ERG's method was more plausible.

The model should not include a remission health state

3.10 In the company's model, patients who did not have a recurrence of uveitis within 2 years were assumed to be in the remission health state, in which their health-related quality of life was the same as the general population. The committee was aware that in the assessment group's model used when developing NICE's technology appraisal guidance on adalimumab and dexamethasone, the remission health state was only used in a scenario analysis. The clinical experts explained that although remission from uveitis is possible, about 30% of people would have a recurrence if treatment were stopped, even if they had not had a recurrence for 2 years. The committee considered it unlikely that everyone who did not have a recurrence of uveitis within 2 years would be in remission. Moreover, even people with uveitis in remission may have lower health-related quality of life than the general population because of bilateral disease or underlying systemic disease. The committee concluded that the model should not include a remission health state.

Results both with and without a transition from on treatment to

permanent blindness should be included

3.11 In the company's model, there was no transition between the on treatment and permanent blindness health states. The ERG added this transition in its base-case analysis, because it was included in the model used when developing NICE's technology appraisal guidance on adalimumab and dexamethasone. The committee was aware that the company's model was consistent with the results of the PSV-FAI-001 trial. The committee concluded that results both with and without this transition would be informative.

Treatment effectiveness in the model

The model should not include a treatment benefit with the fluocinolone acetonide implant after 3 years

3.12 The company's model extrapolated the treatment effect of the fluocinolone acetonide implant beyond the 3-year time horizon of the trial, even though the implant only releases fluocinolone acetonide for 3 years. The clinical experts suggested that for some people there may be residual effects of the treatment after 3 years, and there is an ongoing benefit of having had stable disease for 3 years. The committee agreed that it was possible there may be some benefit after 3 years, but that there was no evidence from the trial to support this. It concluded that the model should not include any treatment benefit with the fluocinolone acetonide implant after 3 years.

Utility values in the economic model

The company's method of incorporating disutility values related to adverse events is more reliable than the ERG's exploratory analyses

3.13 The company used health-related quality-of-life data from the MUST trial because the PSV-FAI-001 trial did not measure it. The MUST trial investigated a higher strength of fluocinolone acetonide implant in the

same indication. To calculate utility values for the on treatment and subsequent therapy health states, the company mapped Visual Function Questionnaire-25 (VFQ-25) data from MUST to the EQ-5D. The ERG highlighted that as well as the implant being a higher strength, the population in MUST was different to that in PSV-FAI-001 (in MUST, 20% of patients had systemic treatment before recurrence, bilateral treatment with the fluocinolone acetonide implant was allowed, and there were fewer people with macular oedema at baseline). For the permanent blindness health state in its base case, the company used a utility value of 0.38, taken from a study by Czoski-Murray et al. (2009). The committee was aware that a utility value of 0.57 from Brown et al. (1999) had been preferred for the permanent blindness health state when developing NICE's technology appraisal guidance on adalimumab and dexamethasone. The committee was also aware that carers' health-related quality of life (see section 3.1) may also be affected, but that it had not been shown evidence to capture this. The ERG highlighted that the company's model did not include disutilities for adverse events. Because the ERG did not have information on the length and severity of each adverse event, it did 2 exploratory analyses assuming a disutility of 0.05 or 0.10 for every adverse event. This increased the cost-effectiveness estimates substantially, but the committee considered these analyses to be speculative and not reliable for decision making. In response to the appraisal consultation document, the company presented an analysis incorporating disutilities for adverse events. It sourced the rates of adverse events from the PSV-FAI-001 trial and the HURON trial (the trial investigating the dexamethasone implant) and the disutility values from a pragmatic literature search. The company included a disutility value of 0.071 for anxiety because of retreatment with multiple intravitreal injections, which hadn't been included in the company's or ERG's original analyses. The committee noted that the disutility values were not sourced from a systematic literature search as preferred in NICE's reference case, but the values were based on EQ-5D, which is preferred. The committee noted that, compared with the ERG's original exploratory analyses, the company's method resulted in lower cost-effectiveness estimates. The committee agreed that because of retreatment with multiple intravitreal injections, a disutility for anxiety should be included and that although the company's disutility of 0.071 may be an overestimate, even a small disutility value would have had a

very favourable effect on the cost-effectiveness results. It concluded that, although there was some uncertainty because of the method of sourcing the disutility values, the company's new method was more reliable than the ERG's exploratory analyses.

Costs and resources in the company's model

Changes to the costs of permanent blindness and monitoring for immunosuppressants have little effect on the cost-effectiveness results

3.14 In the company's model, the costs in the permanent blindness health state were based on those used when developing NICE's technology appraisal guidance on adalimumab and dexamethasone. These were taken from a population with age-related macular oedema and included costs of hip replacement, community care and residential care. The committee noted that the ERG had excluded these costs for people under 65 years in its changes to the model, because uveitis generally affects a younger population than age-related macular oedema and so these costs would be less relevant. The ERG also included costs of a monitoring blood test every 12 weeks while having immunosuppressants in the subsequent treatment health state. The committee concluded that the ERG's changes to the costs were plausible but they did not have a large effect on the cost-effectiveness results.

Cost-effectiveness results

The company's updated cost-effectiveness results are below £30,000 per quality-adjusted life year (QALY) gained but associated with uncertainty

3.15 In response to the appraisal consultation document, the company incorporated its alternative method for modelling disutilities associated with adverse events into the model (see section 3.13). It presented 7 scenarios comparing the fluocinolone acetonide implant with the dexamethasone implant in different combinations of multiple implants.

The company's scenarios included 2 analyses in which 1 dexamethasone implant was given before a fluocinolone acetonide implant, compared with multiple dexamethasone implants, because the clinical experts had said this was plausible (see section 3.2). The company presented all these analyses both with and without the transition between the on treatment health state and the permanent blindness health state (see section 3.11). All analyses included the patient access scheme for the fluocinolone acetonide implant. The results of the company's analyses ranged from the fluocinolone acetonide implant being dominant (that is, it was more effective and costs less), to an incremental cost-effectiveness ratio (ICER) of £29,461 per QALY gained, and most of the ICERs were below £20,000 per QALY gained. The committee noted that using the company's method of modelling disutilities associated with adverse events, which it had agreed was more reliable, none of the company's ICERs presented were above £30,000 per QALY gained. The committee considered that although the company's updated ICERs were within the range normally considered to represent cost-effective technologies, they were associated with a high degree of uncertainty because of the method used to incorporate the dexamethasone implant as a comparator (see section 3.9).

In the ERG's original cost-effectiveness results assuming equal efficacy for both implants, the dexamethasone implant was dominant but some of the committee's preferred assumptions were not included

3.16 The committee then considered the ERG's original base-case results that assumed equal efficacy for both implants, acknowledging the clinical experts' expectation that the effectiveness would be similar. The committee noted that the dexamethasone implant dominated the fluocinolone acetonide implant. The committee considered that these results were also associated with some uncertainty because of the trial results (see section 3.3 and section 3.4). It considered the incremental costs, which are not reported here because they are commercial in confidence. The committee noted that the ERG's original results did not include the disutility for anxiety related to repeated intravitreal injections, and it was reassured that if this had been included it would favour the fluocinolone acetonide implant. The committee concluded that although

the dexamethasone implant dominated the fluocinolone acetonide implant in the ERG's results, the results did not include the committee's preferred assumptions about disutilities for adverse events.

The fluocinolone acetonide intravitreal implant can be recommended as a cost-effective use of NHS resources

3.17 The committee considered the patient experts' statements describing the burden of existing treatments and the effect this had on their quality of life (see section 3.1). The committee agreed that extending treatment choices in this disease area would benefit patients. It took into account the ERG's original estimated cost-effectiveness results, the company's analysis of adverse event disutilities, the clinicians' views and the patients' views. The committee agreed that, had all its preferred assumptions been included in the model, most of the cost-effectiveness estimates would be within the range that NICE normally considers a cost-effective use of NHS resources. It therefore recommended the fluocinolone acetonide intravitreal implant as an option for treating recurrent non-infectious uveitis affecting the posterior segment of the eye.

Innovation

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

3.18 The company considered the fluocinolone acetonide implant to be innovative. It highlighted that the long-lasting design of the implant could lead to benefits such as a reduced treatment burden and more consistent disease control. The clinical experts also suggested that the implant was innovative because of the potential for 3 years of disease control with 1 implant. The committee concluded that the fluocinolone acetonide implant would be beneficial for patients, but it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

Equality considerations

There are no equality issues relevant to the recommendations

3.19 A stakeholder highlighted that the long-lasting design of the fluocinolone acetonide implant could improve adherence to treatment for some people, such as those with dementia or mental health problems. A stakeholder highlighted that that women may benefit more from the fluocinolone acetonide implant because high doses of systemic steroids may adversely affect women's bone density more than men's. Because the committee's recommendation is for the whole population covered by the marketing authorisation, 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 relevant equality issues.

4 Implementation

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

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has recurrent non-infectious uveitis and the doctor responsible for their care thinks that the fluocinolone acetonide intravitreal implant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

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ISBN: 978-1-4731-3485-0

Accreditation