fluocinolone acetonide 190 micrograms intravitreal implant (Iluvien®)
SMC No. (864/13)
Alimera Sciences Limited

05 April 2013 (Issued 10 May 2013)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**fluocinolone acetonide intravitreal implant (Iluvien®)** is not recommended for use within NHS Scotland.

**Indication under review**: treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.

The safety and efficacy of fluocinolone intravitreal implant was assessed in two randomised, double-masked, controlled phase III studies in patients with diabetic macular oedema. Significantly more patients treated with fluocinolone had a clinically significant improvement in visual acuity at two and three years versus sham injection. Subgroup analysis supported this finding in patients with chronic diabetic macular oedema (median duration at least 3 years). Fluocinolone was associated with an increased risk of complications: accelerated cataract formation requiring corrective surgery, and raised intraocular pressure.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

Published on 10 June 2013
Indication
Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.

Dosing Information
One implant administered by intravitreal injection into the affected eye. Administration in both eyes concurrently is not recommended. 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. Retreatments should not be administered unless the potential benefits outweigh the risks. Only patients who have been insufficiently responsive to prior treatment with laser photocoagulation or other available therapies for diabetic macular oedema should be treated with intravitreal fluocinolone.

Treatment should be administered by an ophthalmologist experienced in intravitreal injections. The intravitreal implant insertion should be carried out under controlled aseptic conditions, which include the use of sterile gloves, sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anaesthesia and a broad-spectrum microbiocide should be given prior to the insertion.

Following insertion indirect ophthalmoscopy examination in the quadrant of insertion should be performed to ensure successful placement. Following the procedure, patients should be monitored for potential complications and biomicroscopy with tonometry should be performed between two and seven days after implant insertion. It is recommended that patients are monitored quarterly for complications.

Product availability date
April 2013

Summary of evidence on comparative efficacy
Diabetic macular oedema (DMO) is one of the main causes of visual impairment in diabetic retinopathy, which is a complication of diabetes mellitus. DMO is caused by breakdown of the blood retinal barrier, leading to leakage of fluid and plasma which results in oedema and swelling of the central part of the retina, the macula. The macula mediates high-resolution visual acuity and if DMO is left untreated, loss of visual acuity equivalent to at least two lines (Early Treatment Diabetic Retinopathy Study [ETDRS] ≥10 letters) can occur within two years in approximately 50% of patients.

Fluocinolone acetonide 190 microgram intravitreal implant (Iluvien®) consists of a nonbiodegradeable applicator tube of polymer containing the corticosteroid fluocinolone acetonide (hereafter referred to as fluocinolone) which is released continuously over a period of approximately 36 months. Intravitreal corticosteroids are known to reduce inflammation and swelling in DMO.

Two double-masked studies (FAME A and B) with identical protocols recruited a total of 956 adults with type 1 or 2 diabetes and DMO who had received at least one macular laser
They had best corrected visual acuity (BCVA) ≥19 and ≤68 ETDRS letters (Snellen 20/50 or worse but at least 20/400) in the study eye, and ≥20/400 in the non-study eye. Eligible patients were randomised, with stratification for centre and BCVA (≤49 or >49) in a 1:2:2 ratio, to receive sham injection or intravitreal inserts of fluocinolone 0.2 micrograms/day or 0.5 micrograms/day.1,2

The primary endpoint was the proportion of patients with an improvement from baseline in BCVA of at least 15 ETDRS letters at 24 months. This was assessed within the full analysis set (FAS), which included all randomised patients with last observation carried forward for missing data. Results are presented only for the licensed dose of fluocinolone (0.2 micrograms/day). The table below shows results of the pooled analysis of the FAME studies including the subgroup of patients with DMO for at least three years which provides data most relevant to the licensed indication for chronic DMO. Data at both 24 months (primary outcome) and 36 months (duration of implant) are presented. The per protocol (PP) analysis included all randomised and treated patients with no imputation for missing data, and data after disallowed therapies for DMO or significant protocol violations set to missing. The results indicate that significantly more patients achieved the primary outcome with fluocinolone compared with sham injections, with greater between treatment differences in the subgroup of patients with DMO for at least three years.1,2,3

Table: Results for BCVA increase of ≥15 letters

<table>
<thead>
<tr>
<th>BCVA increase of ≥15 letters</th>
<th>Number (%) responders</th>
<th>Difference, % (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>Fluocinolone 0.2 micrograms/day</td>
<td></td>
</tr>
<tr>
<td>In FAS at 24 months (primary outcome)</td>
<td>30/185 (16)</td>
<td>108/376 (29)</td>
<td>-12 (-20 to -5.5)</td>
</tr>
<tr>
<td>In PP at 24 months</td>
<td>13/86 (15)</td>
<td>78/237 (33)</td>
<td>-18 (-27 to -8.1)</td>
</tr>
<tr>
<td>In FAS at 36 months</td>
<td>35/185 (19)</td>
<td>108/376 (29)</td>
<td>-10*</td>
</tr>
<tr>
<td>In Chronic DMO subgroup at 24 months</td>
<td>15/112 (13)</td>
<td>72/209 (34)</td>
<td>-21*</td>
</tr>
<tr>
<td>In Chronic DMO subgroup at 36 months</td>
<td>15/112 (13)</td>
<td>71/209 (34)</td>
<td>-21*</td>
</tr>
</tbody>
</table>

responders = patients achieving the primary outcome of an improvement of BCVA from baseline of at least 15 letters on ETDRS; difference = sham injection minus fluocinolone 0.2 micrograms; CI = confidence interval; FAS = full analysis set; PP = per protocol; DMO = diabetic macular oedema. * 95% CI not reported

Secondary outcomes included mean change from baseline in BCVA, which was significantly different in the FAS between fluocinolone and sham (4.4 versus 1.7 letters), but not in the PP analysis. Mean change from baseline in centre point macular (foveal) thickness was significantly reduced in the fluocinolone group compared with sham (156 versus 100 micrometres) in the FAS, and the PP results were similar.3
For patients with chronic DMO, the mean change in BCVA from baseline at 36 months was significantly greater with fluocinolone compared with sham (7.6 letters versus 1.8 letters). Although there was a decrease in mean foveal thickness over 36 months, there was no significant difference between fluocinolone and sham.\textsuperscript{2}

Patients could receive retreatment with their assigned study treatment between months 12 and 33 if there was evidence of progression of oedema according to the assessing (masked) investigator. In the chronic DMO subgroup, 24\% of the fluocinolone group and 34\% of the sham group received at least one retreatment of study drug (p-value not reported).\textsuperscript{2} Patients were also permitted to receive laser therapy after week 6 if there was no improvement in DMO from baseline; this could be repeated every three months if required and if the patient had not received retreatment with study drug within the preceding six weeks.\textsuperscript{3} In the chronic DMO subgroup, the proportion of patients who received at least one on-study laser treatment in the study eye was 41\% versus 61\% in the fluocinolone and sham groups respectively (p=0.003).\textsuperscript{2} Patients were allowed to remain in the study even if they received pharmacological treatments for DMO during the study that were not permitted by the protocol. Disallowed treatments included intravitreal or periocular corticosteroid, an anti-vascular endothelial growth factor (anti-VEGF) drug, or vitrectomy. In the chronic DMO subgroup, disallowed treatments were used by 13\% of patients receiving fluocinolone compared with 35\% of patients receiving sham.\textsuperscript{2}

There was no benefit for fluocinolone over sham in health related quality of life in the FAS.\textsuperscript{3}

\textit{Other data were also assessed but remain commercially confidential.}\textsuperscript{*}

\begin{center}
\textbf{Summary of evidence on comparative safety}
\end{center}

In the pooled analysis of the FAME studies, cataract formation was the most frequently reported adverse event in the study eye. Of the patients whose study eye still retained its natural lens at baseline (phakic patients, in whom cataract formation was possible), 82\% (192/235) of the fluocinolone group and 50\% (61/121) of the sham group reported cataracts as an adverse event and this led to surgery in 80\% (188/235) versus 27\% (33/121) respectively. Median time for cataract reporting was 12 months and median time for cataract surgery was 18 months. Almost all patients who developed cataracts in the fluocinolone group had surgery compared with approximately half of those who developed cataracts in the sham group.\textsuperscript{2} Cataract progression was considered by the study investigators to be universal and inevitable. Posterior subcapsular cataract is the most common type of corticosteroid-related cataract and may be associated with greater risk of surgical complications.

Patients with baseline intraocular pressure (IOP) >21mmHg or using IOP-lowering medication were excluded from the FAME studies. Raised IOP requiring medication was more common in the fluocinolone group than in the sham group: 38\% (144/375) versus 14\% (26/185) respectively. This necessitated laser trabeculoplasty in 1.3\% (5/375) of the fluocinolone group versus no patients in the sham group, and incisional IOP-lowering surgery in 4.8\% (18/375) versus 0.5\% (1/185) patients respectively.\textsuperscript{2}

Endophthalmitis occurred in 0.2\% (2/1,022) of all fluocinolone injections administered during the studies and both cases were in patients receiving the licensed dose.\textsuperscript{3,4}

\textit{Other data were also assessed but remain commercially confidential.}\textsuperscript{*}
Summary of clinical effectiveness issues

Fluocinolone (Iluvien®) is the first corticosteroid intravitreal implant to be licensed for the treatment of DMO. There are currently no other medicines licensed for the treatment of vision impairment associated with chronic DMO considered insufficiently responsive to available therapies (laser and ranibizumab).

Two identical dose-finding studies (FAME A and B) were presented as a pooled analysis in which the subgroup of patients with baseline DMO of at least three years duration was considered to be most relevant to the licensed population (chronic DMO). Within this subgroup there was a significant and clinically relevant improvement for fluocinolone versus sham in the proportions of patients who achieved an increase in BCVA of at least 15 ETDRS letters. There was no quality of life benefit with fluocinolone which may be due to the fact that most (77%) patients were treated in their worse seeing eye. The clinical benefit is tempered by the high rate of complications associated with the corticosteroid intravitreal implant: acceleration of cataract formation (and subsequent need for corrective surgery) and increases in IOP.

One limitation of the FAME studies is that the population had less severe DMO than would be eligible for treatment with fluocinolone in practice, as patients were not required to have had an insufficient response to all available treatments for DMO. The use of laser photocoagulation, corticosteroid and anti-vascular endothelial growth factor (anti-VEGF) treatments as rescue therapy provides further evidence that patients had not already failed on all available treatments. Another limitation is that the evidence is based on a subgroup of the full study population (patients who had DMO for at least three years at randomisation). These patients were more likely to have had previous cataract surgery than those who had DMO for less than three years and to have a larger area of cystoid macular changes. The high incidence of cataract formation complicated the evaluation of visual acuity.

The relevant comparator is best supportive care as the marketing authorisation for intravitreal fluocinolone places it as end of line treatment after other available therapies. SMC clinical experts advised that there is an unmet need for a therapy for patients who are unresponsive to laser and anti-VEGF therapies. They also highlighted the inevitable side effect profile associated with intravitreal steroids.

The fluocinolone intravitreal implant requires to be inserted by an ophthalmologist experienced in intravitreal injections under controlled aseptic conditions. Adequate anaesthesia and a broad-spectrum antibiotic should be given prior to the insertion. Monitoring is required several days after insertion and every three months thereafter. The formulation is designed to release fluocinolone for at least three years. If raised IOP occurs and does not respond to IOP-lowering medications or procedures, the implant has to be removed by vitrectomy. The long-term safety implications of retention of the non-biodegradable implant inside the eye are not known. An advantage of this long acting implant formulation is that regular repeated injections are not required. The company submission states that it is likely that the mean time to administration of the second insert will be between three and four years. However, the probability of retreatment before this time is not known. For patients receiving the licensed dose of fluocinolone, 26% in the full pooled study and 24% in the chronic DMO subgroup had been retreated by month 33.2

Other data were also assessed but remain commercially confidential.*
Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing fluocinolone with best supportive care (BSC) in patients with visual impairment due to chronic DMO after an inadequate response to prior therapy. For this patient population the comparator is appropriate. A Markov model was used to estimate changes in best corrected visual acuity across 5 letter health states based on three year data from the FAME studies out to a 15 year time horizon. To reflect clinical practice, the company assumed that of the chronic DMO patients in the model 40% would be treated in their better seeing eye (BSE), 20% in the worse seeing eye (WSE) and 40% would receive bilateral treatment.

Patient level data from the FAME studies for fluocinolone and for the BSC comparator (proxied by sham injection) for the chronic DMO sub-population were used to provide 3-monthly transition probabilities between the 5 letter health states for the first three years. Only patients who responded to fluocinolone at 3 years were assumed to receive a re-treatment and benefit from further treatment over BSC. Responders were defined as patients who had experienced at least a 10 letter improvement in BCVA. The extrapolation to 15 years utilised the last 12 months of FAME-based transition probabilities, with the fluocinolone probabilities applied to responders, and BSC/sham probabilities applied to non-responders and BSC patients. As many of the fluocinolone patients had undergone cataract surgery in the first 24 months of the FAME studies, the last 12 months trial data was used as the basis of the extrapolation to minimise the confounding impact of improved short term visual acuity and hence HRQoL outcomes related to the surgery.

Utility values relating to BCVA health states were derived from a published study using time trade-off methods in 72 age related macular degeneration patients from the US. The values from this study were based on the BSE being treated. There are limited data available for assessing the utility change to apply if the the WSE is treated. The company used an estimate of a utility gain for the WSE being treated that was 50% that of the benefit with the BSE treated, based on an estimate from one of the published studies reviewed. An incremental benefit for the WSE in addition to the BSE utility was also assumed for patients receiving bilateral treatment. No account has been taken of the additional disutility associated with cataract surgery and other procedures for adverse events.

The cost of the fluocinolone implant and administration was included. Patient discontinuation due to death or other reasons was accounted for, but no-retreatment during the first three years was allowed despite a proportion of chronic DMO patients receiving more than one treatment in the FAME studies. Resource use associated with patient monitoring, the use of laser and off-label therapies including anti-VEGF therapies used alongside fluocinolone or BSC were included. Expert opinion was used to estimate resource use for patient monitoring covering use of optical coherence tomography, fluorescein angiography and outpatient visits. The costs associated with treatment of adverse events, predominantly cataract surgery and elevated IOP for fluocinolone, were included.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. As SMC has not recommended use of the medicine, however, the PAS cannot be implemented in NHS Scotland. Under the PAS, a simple price discount was offered on the cost of the medicine. With the PAS, the incremental cost-effectiveness ratio (ICER) was £23,546 per QALY gained. Sensitivity analysis demonstrated that the results were quite sensitive to
assumptions relating to the proportion treated in BSE/WSE or bilaterally, with the ICER increasing with higher proportions treated in the WSE.

The main limitations of the all chronic DMO patient analysis are:

- Based on feedback from SMC clinical experts, there is uncertainty over the proportion of patients treated in the WSE in clinical practice. The model assumed 20% of patients had the WSE treated and the results were sensitive to this variable. Increasing the proportion treated in the WSE to 40% in the model leads to a higher ICER. In addition, the most favourable published utility estimates have been used for BCVA health states for fluocinolone versus BSC outcomes, and there is uncertainty over the appropriate adjustment to apply relative to the BSE if the WSE is treated (utility benefits that are 50% of the BSE benefits have been applied in the base case). Applying more pessimistic BCVA utilities potentially increases the ICER to above £30/QALY gained even with PAS applied, especially if combined with a lower WSE adjustment of 30% consistent with that applied in other HTA assessments for DMO. Also, assuming no additional utility associated with treating the WSE in bilateral treatment, which is more appropriate than assuming benefits for WSE treatment on top of BSE utility gains, increases the ICER.

- There is high use of cataract surgery in fluocinolone treated patients which could confound the use of the trial data as the basis of extrapolation. The company has used only the last 12 months of trial data to try to minimise this bias, but some patients received cataract surgery in this period. As visual acuity outcomes are improved by cataract surgery, the impact this has on longer-term outcomes and the ICER for fluocinolone is uncertain.

- The model does not allow for re-treatment within the first three years. However, the SPC allows retreatment after 12 months if there is an impact of worsening DMO on vision or retinal thickness. Including re-treatment for a proportion of patients at 12 months would increase costs associated with additional fluocinolone implants, but there is also uncertainty over the impact on outcomes. The company stated that they would not expect re-treatment to occur before 36 months in clinical practice. However, an analysis supplied assuming that the 23.9% of chronic DMO patients who were re-treated in the clinical trials received a second treatment at the start of year 2 in the model, increased the ICER.

- Additional scenario analysis requested indicated upwards uncertainty in the ICER, with the results exceeding £40k/QALY with PAS when combining alternative published BCVA utilities with lower WSE adjustment (30%) and a higher proportion of patients treated in the WSE (40%) than assumed in the model.

- There may also be limitations with the clinical data used as the patients in the studies appear to have less severe disease than those expected to be treated in practice (see the clinical effectiveness section).

The submitting company provided some further analysis prior to the SMC meeting to show the cost-effectiveness of fluocinolone intravitreal implant in a subgroup of patients with more severe chronic DMO, namely patients whose visual acuity was 20/80 or worse. The information provided required more in depth analysis by the company and therefore SMC was not able to fully appraise this new positioning at this late stage in the process.
Overall, due to a high ICER and uncertainties in key variables, cost-effectiveness has not been demonstrated. It is SMC policy to include the estimated QALY gain in the detailed advice document for all submissions. The PAS for fluocinolone includes a discount to the NHS that is commercial in confidence and the submitting company has advised that publication of the QALY gain, when considered with other cost-effectiveness data in the public domain, could reveal the level of discount. For this reason SMC is unable to publish the estimated QALY gain.

*Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Royal College of Ophthalmologists updated their “Diabetic Retinopathy Guidelines” in December 2012. These state that in patients with phakic eyes (eyes that still retain their natural lens) with visual impairment secondary to DMO with visual acuity of 24 to 78 letters, the recommended treatment is intravitreal anti-VEGF with or without photocoagulation laser. In eyes that do not respond to other treatments, intravitreal fluocinolone implant may be considered, but bearing in mind the potential side-effects.

In patients with pseudophakic eyes (that have an artificial lens following cataract removal) with visual impairment secondary to DMO with visual acuity of 24 to 78 letters, the recommended treatment is intravitreal anti-VEGF treatment or intravitreal triamcinolone (preservative–free) with or without adjunctive laser may also be considered. Intravitreal fluocinolone implant may be considered if available, and the eye is unresponsive to other treatments. If these patients have visual acuity below 24 letters observation may be appropriate, especially if longstanding and there is no response to previous laser, or if considerable macular ischaemia. Otherwise the clinician may consider anti-VEGF treatment or intravitreal steroid after careful consultation and consent.7

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 116: “Diabetes” in 2010. It states that modified ETDRS grid laser photocoagulation should be used for patients with clinically significant macular oedema in the absence of significant macular ischaemia. The recommendations for pharmacological treatment of diabetic macular oedema pre-date recently licensed treatments.8

Additional information: comparators

The licensed indication only allows the use of intravitreal fluocinolone as the last line of medical treatment. Other treatments that have been used for diabetic DMO in Scotland include laser photocoagulation, the anti-vascular endothelial growth factor (anti-VEGF) drugs bevacizumab, (not licensed for intravitreal use), the recently available ranibizumab and the intravitreal corticosteroids, triamcinolone and dexamethasone which are not licensed for this indication.
Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost over 3 to 4 years £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluocinolone acetonide</td>
<td>One implant (releases 0.2 microgram drug daily ) to be inserted intravitreally once every 3 years. Retreatment is permitted after 12 months if required.</td>
<td>5,500 to 22,000</td>
</tr>
</tbody>
</table>

Costs from company submission and based on one or two treatments in one or both eyes.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 12,177 in Year 1 rising to 12,631 in Year 5 to which estimates of uptake were applied. Without the PAS, the gross impact on the medicines budget was estimated to be £1.531m in year 1 and £8.312m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £1.233m in year 1 and £6.367m in year 5. However, given that the comparator treatment is best supportive care, it is unlikely that cost-offsets of this magnitude would arise.

*Other data were also assessed but remain commercially confidential.*
References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.


4. Alimera Sciences Limited. Iluvien 190 micrograms intravitreal implant applicator summary of product characteristics 04.05.2012


7. The Royal College of Ophthalmologists Diabetic Retinopathy Guidelines December 2012


This assessment is based on data submitted by the applicant company up to and including 18 March 2013.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.
Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.