Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

Resubmission

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

Alimera Sciences Limited

10 January 2014

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 Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

fluocinolone acetonide intravitreal implant (Iluvien®) is accepted for restricted use within NHS Scotland.

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

SMC restriction:
- only in patients in whom the affected eye is pseudophakic (has an artificial lens after cataract surgery) and;
- retreatment would take place only if the patient had previously responded to treatment with fluocinolone acetonide and subsequently best corrected visual acuity had deteriorated to less than 20/32.

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 acetonide had a clinically meaningful improvement in visual acuity at two and three years versus sham injection. Subgroup analyses supported this finding in patients with chronic diabetic macular oedema (median duration at least three years) and in patients who were pseudophakic at baseline. Raised intraocular pressure is an important safety issue.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of fluocinolone. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman, Scottish Consortium Medicines

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 acetonide.

It 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 macula which is the central part of the retina. 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 non-biodegradable 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.

The submitting company has requested that SMC considers fluocinolone when positioned for use in patients who are pseudophakic (have an artificial lens inserted after cataract surgery); that only one treatment of fluocinolone per eye is administered in the first three years; and that

retreatment in subsequent 3-year cycles would take place only if the patient had responded to treatment before and had best corrected visual acuity (BCVA) less than 20/32.

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 treatment more than 12 weeks before study entry and had mean foveal thickness at least 250 micrometres. They had 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 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]

In the subgroup of chronic DMO patients who were pseudophakic at baseline, significantly more fluocinolone than sham patients achieved the primary outcome at 36 months. Some of these patients received retreatment.[5]

Table: Results for BCVA increase of ≥15 letters[1,2,4,5]

BCVA increase ≥15 letters	**Number (%) responders**		**Difference, % (95% CI)**	**p-value**
	Sham	**Fluocinolone 0.2 micrograms/day**		
FAS (24 months) (primary outcome)	30/185 (16)	108/376 (29)	-12 (-20 to -5.5)	0.002
FAS (36 months)	35/185 (19)	108/376 (29)	-10 (-17.1 to -2.5)	0.018
Chronic DMO patients at 36 months	15/112 (13)	71/209 (34)	-21 (-29.6 to -11.6)	<0.001

responders=patients with an improvement of BCVA from baseline of ≥15 letters on ETDRS; difference = sham injection minus fluocinolone 0.2 micrograms; CI=confidence interval; NR=not reported

The secondary outcome of mean change from baseline in BCVA at 36 months was significantly improved with fluocinolone compared with sham in patients with chronic DMO, (7.6 versus 1.8 ETDRS letters) p=0.004.

Patients could receive retreatment with their assigned study therapy between months 12 and 33 if there was evidence of progression of oedema according to the assessing (masked) investigator. 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.[3]

There was no benefit for fluocinolone over sham in health related quality of life in the FAS.[3]

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

Summary of evidence on comparative safety

In the pooled analysis of the FAME studies, cataract formation was the most frequently reported adverse event in the study eye and occurred in 82% (192/235) of the fluocinolone group and 50% (61/121) of the sham group who were phakic (retained their natural lens) at baseline 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.[2] The proposed selective indication includes only pseudophakic patients who are not at risk of cataract formation.

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.[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.[3,7]

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). The selective indication under review includes only patients who are pseudophakic. It also stipulates that there be only one treatment of fluocinolone acetonide per eye in the first three years; and that retreatment in subsequent 3-year cycles would take place only if the patient had responded to treatment before and had BCVA less than 20/32.

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, a significantly higher proportion of patients treated with fluocinolone versus sham achieved a clinically relevant improvement in BCVA of at least 15 ETDRS letters. The selective population under review corresponds to a smaller subgroup of patients with chronic DMO who were pseudophakic at baseline in which significantly more fluocinolone than sham patients achieved an increase in BCVA of at least 15 letters. [5] 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.[3]

One limitation of the FAME studies is that the population may have 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.

Another limitation is that the evidence for the proposed selective indication is based on a post-hoc subgroup equating to about 25% of the full study population (patients who, at baseline, had DMO for at least three years and had cataract surgery in the study eye). Within the chronic DMO subgroup, patients who were pseudophakic at baseline had broadly similar patient and disease baseline characteristics to those who were phakic at baseline. [5]

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. The proposed selective indication removes concerns about cataract formation; however increased IOP is an important safety issue which has been highlighted by clinical experts consulted by SMC. If raised IOP occurs and does not respond to IOP-lowering medications or procedures, the implant has to be removed by vitrectomy. 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 implant 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. The long-term safety implications of retention of the non-biodegradable implant inside the eye are not known.[7]

*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 pseudophakic 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 BCVA across five 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 a subgroup of chronic pseudophakic DMO patients from the FAME studies for fluocinolone and for the BSC comparator (proxied by sham injection) were used to provide 3-monthly transition probabilities between the five letter health states for the first three years. Only patients who responded to fluocinolone at three years and whose visual acuity then declined to below 20/32 vision (90 letters corresponding to mild vision impairment) were assumed to receive a retreatment 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 30 months of FAME-based transition probabilities for the pseudophakic sub-population, with the fluocinolone probabilities applied to responders, and BSC/sham probabilities applied to non-responders and BSC patients.

Utility values relating to BCVA health states were derived from a published study (Brown 2000) using time trade-off methods in 72 age related macular degeneration patients from the US. [8] 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 WSE is treated. The company applied an estimate of a utility gain for the WSE being treated that was 30% that of the benefit with the

BSE treated, a value that has been accepted in previous health technology assessments in the UK. An incremental benefit for the WSE in addition to the BSE utility was also assumed for patients receiving bilateral treatment.

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 elevated IOP for fluocinolone in the pseudophakic patient population, were included. There was no impact associated with cataract surgery as the pseudophakic sub-population of chronic DMO patients had received prior cataract surgery.

A patient access scheme (PAS) has been submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation 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 £9,464 per quality-adjusted life year (QALY) gained, with an incremental cost of £4,215. An alternative base case analysis demonstrated that the results were quite sensitive to the source of utility estimate for BSE. Using relatively pessimistic values from an alternative published source (Brown 1999) increased the ICER up to £16.7k per QALY with PAS. A range of scenarios were explored including assuming retreatment in all responders at 3 years, increasing the proportion treated in the WSE, increasing the utility gain in the WSE and assuming no WSE benefit in bilateral treatment. The ICERs were below £12k per QALY with PAS. When Brown 1999 utilities were applied to these analyses, in the majority of scenarios considered the ICERs were between £13k - £23k per QALY with the PAS applied.

The main limitations of the economic evaluation were as follows:

- The company requested the SMC to consider restricting fluocinolone to a maximum of one treatment per eye in the first 3 years. This may not reflect clinical practice, especially as the SPC allows retreatment after 12 months if there is an impact of worsening DMO on vision or retinal thickness and 21% of the pseudophakic patient population were retreated in the FAME trials. Therefore, such a restriction is unlikely to be feasible to monitor in practice. A scenario analysis provided by the company including retreatment between 12 months and 3 years, and also assuming a higher proportion of patients are treated in the WSE in clinical practice, increased the ICER to between £14.6k and £25.5k/QALY gained, dependent on BSE utilities used.
- A limitation with the clinical data is the relatively small patient numbers for the target population of pseudophakic patients as a basis for assessment and extrapolation of the benefits of fluocinolone. There were also a number of other limitations with the clinical trial data as have been noted above.

Despite some remaining uncertainties the ICERs with PAS in a range of scenario analyses appear acceptable in the chronic pseudophakic DMO patient population. Therefore, the economic case has been demonstrated.

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

Summary of patient and public involvement

A Patient Interest Group Submission was made from RNIB

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 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 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.[10]

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.[11]

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

Drug	Dose Regimen	Cost over 3 years (£)
Fluocinolone acetonide	**One implant (releasing 0.2 microgram drug daily) to be inserted intravitreally once every 3 years.**	**5,500 to 11,000**

Costs from company submission and based on one treatment in one or both eyes and assuming no retreatment within three years.

Additional information: budget impact

The submitting company estimated the chronic pseudophakic DMO population eligible for treatment to be 179 in year 1 rising to 186 in year 5 to which estimates of uptake of 26.7% in year 1, 40% in year 2, and 80% in year 3, 4 and 5 were applied.

Without the PAS, the gross impact on the medicines budget was estimated to be £353k in year 1, £481k in year 3, and £138k in year 5.

As no other drugs were assumed to be displaced, the net medicines budget impact is estimated to be the same as the gross cost. The lower costs beyond year 3 are due to a large proportion of currently untreated patients receiving a fluocinolone implant spread over years 1-3. However, feedback from SMC clinical experts indicated a relatively low uptake is expected, hence the budget impact estimates may be overestimated.

References

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

1. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Opthalmology 2011;118:626-35
2. Campochiaro PA, Brown DM, Pearson A, et al Sustained Delivery Fluocinolone Acetonide Vitreous Inserts Provide Benefit for at Least 3 Years in Patients with Diabetic Macular Edema. Opthalmology 2012 Jun 21. [Epub ahead of print]
3. Iluvien 190micrograms intravitreal implant applicator. Public Assessment Report (PAR) Medicines and Health Care products and Regulatory Agency (MHRA); June 2012.
4. Alimera Sciences Limited. Iluvien 190 micrograms intravitreal implant applicator summary of product characteristics 04.05.2012
5. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. Arch Ophthalmol. 2000 Jan;118(1):47-51
6. Brown GC. Vision and quality-of-life. Trans Am Ophthalmol Soc 1999;97:473-511
7. The Royal College of Ophthalmologists Diabetic Retinopathy Guidelines December 2012 update to section 14.3.4 in accordance with College statement on intravitreal injections
8. Scottish Intercollegiate Guideline (SIGN), Management of Diabetes, A national clinical guideline. SIGN 116; 2010.

This assessment is based on data submitted by the applicant company up to and including 12 December 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. 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.