Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2260

fluocinolone acetonide 190 micrograms intravitreal implant (Iluvien®)

Alimera Sciences

7 August 2020

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

fluocinolone acetonide (Iluvien®) is accepted for use within NHSScotland.

Indication under review: prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye.

In a double-blind, phase III study in patients with recurrent non-infectious uveitis affecting the posterior segment of the eye, fluocinolone acetonide intravitreal implant reduced the number of recurrences of uveitis compared with sham injection.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

For the prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye.[1]

Dosing Information

The recommended dose is one fluocinolone acetonide implant in the affected eye. Administration in both eyes concurrently is not recommended. Each implant releases fluocinolone acetonide for up to 36 months. There are no data available to support the retreatment of patients with an additional implant.

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

Please see Summary Product Characteristics (SPC) for further information including the injection procedure.[1]

Product availability date

22 March 2019

Summary of evidence on comparative efficacy

Iluvien® is a sustained-release intravitreal drug delivery system that releases submicrogram levels of fluocinolone acetonide, a glucocorticoid, in the vitreous humour for up to 36 months.[2] Corticosteroids inhibit the inflammatory response by inhibition of mediators such as prostaglandins, leukotrienes and vascular endothelial growth factor.[1]

Evidence for this indication is from the multicentre, randomised, double-blind, phase III PSV-FAI-001 study. This evaluated the efficacy and safety of fluocinolone acetonide intravitreal implant compared with a sham injection. The study included 129 adults with ≥1 year history of unilateral or bilateral recurrent non-infectious uveitis affecting the posterior segment of the eye with or without anterior uveitis. At enrolment, the study eye had <10 anterior chamber cells per high power field, a vitreous haze ≤ grade 2 and visual acuity of the study eye was at least 15 letters on the early treatment diabetic retinopathy study (ETDRS) chart. Standard systemic or topical treatment to manage uveitis was permitted at study entry provided this was stopped within the 3 months after the study treatment began.[2, 3]

Eligible patients were randomised in a 2:1 ratio to receive a fluocinolone acetonide 190micrograms intravitreal implant (n=87) or sham injection (n=42) into the study eye. The fluocinolone acetonide implant was injected into the vitreous cavity via a pre-loaded applicator.

The sham injection was a blunt needle pressed against the sclera with pressure exerted to mimic the injection procedure. Treatment randomisation was stratified by systemic treatment for uveitis control at study entry and type of treatment (corticosteroid or immunosuppressant). Recurrence of uveitis in either group was treated with intraocular or periocular corticosteroid injections or topical treatments. Systemic immunosuppressants or corticosteroids were used following local or topical treatment failure. This was considered reflective of standard treatment.[2, 3]

The primary analysis was performed at month 6 and secondary analyses were performed at month 12 and month 36 in the intention to treat population (ITT). The primary outcome was the difference between study groups in the proportion of participants who had no recurrence of uveitis by month 6. A recurrence was imputed if a participant did not complete the month 6 eye examination for any reason or, if they received a prohibited systemic or topical medication in the study eye at any time during the study prior to month 6. Prohibited medication included oral, systemic, injectable or topical corticosteroids or systemic immunosuppressants.[2, 3]

At 6 months, the proportion of patients experiencing a recurrence of uveitis in the study eye was significantly lower in the fluocinolone acetonide group than in the sham injection group. Key secondary outcomes assessed at month 36 favoured fluocinolone acetonide implant over sham injection. See Table 1 for further details [2, 3]

Table 1: Primary and key secondary outcomes of PSV-FAI-001.[1,2,4]

	Fluocinolone acetonide n=87	Sham injection n=42
Primary outcome		
Recurrence within 6 months, % (n)	28% (24)	91% (38)
No recurrence within 6 months, % (n)	72% (63)	10% (4)
Odds ratio (95% CI) p-value	24.9 (8.0 to 77.4) p<0.001	
Key secondary outcomes at 36 months (unless otherwise stated)		
Recurrence rate, % (n)		
12 months	38% (33)	98% (41)
Odds ratio (95% CI)	67.1 (95% CI: 8.8 to 511.1)	
36 months	66% (57)	98% (41)
Odds ratio (95% CI)	21.6 (95% CI: 2.8 to 164.7)	
Cumulative recurrences, n	149	223
Median per patient, n	1	5
Median time to first recurrence, days	657	70.5

CI=Confidence interval, BCVA=best corrected visual acuity, ETDRS=early treatment diabetic retinopathy study.

Subgroup analysis of participants affected by uveitis in the fellow eye showed a greater proportion in the fluocinolone acetonide group reported a recurrence of uveitis in the fellow eye than the sham injection group at month 6 (80% versus 65%), month 12 (86% versus 74%) and month 36. [2, 4, 5]

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

Summary of evidence on comparative safety

The Medicines and Healthcare products Regulatory Agency (MHRA) concluded in the Public Assessment Report (PAR) that the potential risks associated with fluocinolone acetonide appear generally manageable. Overall the most common adverse events (AEs) were cataract, raised intraocular pressure and conjunctival haemorrhage. Long-term use of corticosteroids is known to cause cataract and raised intraocular pressure. The Summary of Product Characteristics (SPC) states the presence of pre-existing glaucoma as a contraindication and recommends intraocular pressure is monitored regularly throughout the treatment course.[1, 2]

Any treatment-emergent ocular AE in the study eye was reported by 80% (70/87) of participants in the fluocinolone acetonide group and 93% (39/42) in the sham injection group during 12 months of follow-up. In the fluocinolone acetonide and sham injection groups respectively, participants with a reported ocular treatment-related serious AE in the study eye were 10% and 17%.

Approximately half of the participants (49% and 52%) in both treatment groups experienced a non-ocular AE during the first 12months of the study.[3]

The most frequently reported treatment-emergent AEs affecting the study eye in the fluocinolone acetonide or sham injection group were cataract (28% versus 4.8%), increased intraocular pressure (26% versus 26%), reduced visual acuity (20% versus 12%), eye pain (13% versus 17%), conjunctival haemorrhage (13% versus 10%), uveitis (10% versus 40%), conjunctival haemorrhage (13% versus 10%), vitreous floaters (7% versus 12%), macular oedema (5.7% versus 33%), cystoid macular oedema (9.2% versus 19%). Adverse events considered serious in the respective groups were cataract (4.6% versus 0%), macular oedema (0% versus 4.8%), non-infectious endophthalmitis (0% versus 4.8%) and uveitis (1.1% versus 4.8%).[3]

At 36 months, surgery to control intraocular pressure in the study eye was required in 5.7% of the fluocinolone acetonide group and 12% of the sham injection group. In participants with phakic lens status in the study eye, 74% (31/42) in the fluocinolone acetonide group and 24% (5/21) required ≥1 cataract surgery in the study eye.[2, 4]

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

Summary of clinical effectiveness issues

Uveitis is a condition causing inflammation of the uvea (vascular area between the retina and sclera of the eye). It affects 2 to 5 in every 10,000 people in the UK each year. It typically affects those aged 20 to 59 but can develop at any age. Men and women are affected equally. Potential causes of uveitis include systemic autoimmune disorders, less commonly infection or trauma to the eye and rarely neoplasia. Posterior uveitis causes inflammation of the posterior vitreous, choroid, retina, or optic nerve head and is potentially sight-threatening. Recurrent uveitis is described as repeated episodes, separated by periods of inactivity without treatment, for more than 3 months. There are no national guidelines for the treatment of uveitis. The aim of initial treatment is rapid control of active inflammation and corticosteroids are commonly used to achieve this. Some patients will require long-term maintenance treatment to prevent recurrence of inflammation. Any underlying autoimmune disorders should be managed appropriately.[6]

Fluocinolone acetonide is the only licensed medicine specifically for prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. Dexamethasone intravitreal implant (duration of effect around 6 months) is licensed for treatment of inflammation of the posterior segment of the eye presenting as non-infectious uveitis. It is recommended as a treatment option in patients with active disease (that is, current inflammation in the eye), and worsening vision with a risk of blindness.[10] Adalimumab is licensed for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. It is recommended as a treatment option in patients

with active disease, inadequate response or intolerance to immunosuppressants, systemic disease or both eyes are affected (or one eye is affected if the second eye has poor visual acuity), and worsening vision with a high risk of blindness.[10] Alternative immunomodulatory therapies are used off-label and may include tacrolimus, mycophenolate mofetil and infliximab.

Clinical experts consulted by SMC considered that fluocinolone acetonide intravitreal implant fills an unmet need in this therapeutic area as it provides a longer term treatment option.

The PSV-FAI-001 study demonstrated that fluocinolone acetonide intravitreal implant in addition to standard treatment significantly reduced the proportion of patients who experienced a recurrence of uveitis in the study eye at 6 months in comparison to standard treatment alone. Furthermore, recurrence remained lower at 36 months. Secondary outcomes favoured fluoinolone acetonide over the sham injection including time to first uveitis recurrence, improvement in visual acuity, reduction in macular oedema and use of adjunctive corticosteroids or immunosuppressants. In bilateral disease, more participants experienced a recurrence of uveitis in the fellow eye in the fluocinolone group. The submitting company suggest this may be because of lower usage of systemic treatments in this group.

A large proportion of recurrences of uveitis were imputed for the primary and secondary outcomes; therefore the recurrence rate is likely to be overestimated. Most of the imputations were because of concomitant treatment with prohibited medication. The study did not report the indication for prescription of the medicines; it is therefore unclear the proportion used to treat uveitis and related underlying conditions and unrelated indications. Sensitivity analyses performed around missing data supported results from the primary analyses.

No health-related quality of life data were reported in the PSV-FAI-001 study therefore, there is uncertainty on how treatment with a fluocinolone acetonide implant will impact patients' quality of life.[2]

Recurrent non-infectious posterior uveitis is a chronic disease that often requires retreatment for long-term management. There are no data to support retreatment with an additional implant for this indication.[1] There are also no data for patients with moderate to severe uveitis graded by vitreous haze 3+ or 4+.[2]

There are no data for fluocinolone acetonide intravitreal implant relative to an active comparator. In practice, treatments for patients with current inflammation may include dexamethasone intravitreal implant and immunomodulatory therapies such as adalimumab. The submitting company state that an indirect treatment comparison with dexamethasone was inappropriate because of heterogeneity between the respective pivotal studies, and a naïve treatment comparison was not performed due to the lack of clinical efficacy data available to support a reliable evaluation.

The introduction of a fluocinolone acetonide intravitreal implant with its prolonged duration of action may reduce the number of ocular injections and administration-associated adverse events. It may also result in fewer courses of acute systemic corticosteroids to treat acute flares.[2]

Clinical experts consulted by SMC generally considered fluocinolone acetonide implant to be a therapeutic advancement because of its longer duration of action, although it was noted that once inserted into the eye treatment cannot be stopped. They consider its place in therapy to be for patients whose disease requires long-term treatment in whom systemic immunosuppression may be inappropriate, or those who would benefit from reduced frequency of administration of ocular steroid injections. Its introduction may benefit the service through fewer clinic appointments to administer repeated injections.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis for the prevention of relapse in recurrent non-infectious uveitis based on the PSV-FAI-001 clinical study. The analysis compared outcomes following insertion of a fluocinolone acetonide implant at baseline with standard treatment, which included: systemic corticosteroids or immunosuppressants, topical steroids, intraocular pressure reduction therapy, cataract removal and other elective ocular surgery, and treatment of recurrence of uveitis.

The submitting company based their analysis on a Markov cohort state transition cost-effectiveness model with four states in the base case, supplemented with a fifth in scenario analysis. Patients enter the model in an 'on-treatment' state (fluocinolone acetonide or standard treatment), from which they may transition on recurrence to subsequent therapy or death. Patients in the subsequent therapy state are at risk of permanent blindness or death. Once blindness has occurred patients remain in this state until death. Patient cannot move directly from on-treatment (fluocinolone acetonide or standard treatment) directly to permanent blindness. A scenario option in the model considered a state of remission for patients who remain recurrence-free after two years. The time horizon for the analysis was 51 years (lifetime).

The model considers treatment with a fluocinolone acetonide implant in a single eye, though many patients in PSV-FAI-001 had bilateral disease. The implant is designed to release fluocinolone acetonide for 36 months. At this point, no re-treatment is considered in the model, and patients exit the on-treatment or recurrence-free state in line with the standard treatment arm projections. In each arm recurrence is modelled based on the endpoint in PSV-FAI-001 including imputed recurrence. Due to a sudden drop in the recurrence-free curve in the fluocinolone acetonide implant arm at 120 days the periods before and after this point are modelled separately for fluocinolone acetonide. Extrapolation in the submitted base case used an exponential distribution for fluocinolone acetonide and log-logistic for standard treatment. Rather than adopt hazards for recurrence based on the standard treatment arm after the 36 month period of effect for fluocinolone acetonide implant, the model imposed the absolute standard treatment arm recurrence free survival. Once patients have suffered a recurrence and are off

treatment they are at risk of permanent blindness. The probability of this is based on a retrospective analysis of insurance claims data in the USA of patients with NIP-PU, where the incidence at 10 years was 6.6%.[7]

Utility estimates for on and off treatment (0.818 and 0.759 respectively) were based on mapping to EuroQol EQ-5D from VFQ-25 scores in the Multicenter Uveitis Steroid Treatment (MUST) study that compared systemic corticosteroid therapy (and immunosuppression when indicated) against to fluocinolone acetonide implant placement.[8] Where these estimates were higher than population values by age, the population value took precedence. No account was taken of the impact of adverse events on quality of life. The higher on-treatment utility estimate has negligible effect beyond 36 months as there is no re-treatment, but permanent blindness was associated with a utility of 0.38.[9]

Implant acquisition and administration costs, monitoring, management of adverse events, adjunctive medicines (by treatment arm), and costs of subsequent therapies were included. One-off costs due to transition to permanent blindness, and those associated with the state of blindness were also included. These included costs associated with hip-replacement and community and residential care assigned to patients in the permanent blindness state irrespective of age.

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 NHSScotland. Under the PAS a discount was offered on the list price of the medicine.

The base case incremental cost-effectiveness ratio (ICER) with the PAS was £15,393 per quality adjusted life-year (QALY). A range of sensitivity and scenario analyses were provided by the submitting company as summarised in table 2.

Table 2: Scenario analyses (with PAS)

	Scenario	**ICER**
	Base case	**£15,393**
1	Time horizon: 3 years	£35,378
2	Time horizon: 20 years	£19,484
3	Blindness utility 0.57	£19,680
4	Include remission	£13,059
5	Annual rates of blindness 0.0038	£22,023
6	Annual rates of blindness 0.0374	dominant
7	Exponential recurrence free survival for standard treatment arm *	£14,413
8	Equal adjunctive medication costs in both arms	£15,242
9	Reduced costs of blindness age < 65	£19,114
10	#7, #8 and #9 combined	£19,943
11	#7, #8 and #9 combined and blindness utility 0.47	£22,235
12	#7, #8 and #9 combined with lower 95% confidence limit for FAc recurrence free survival	£24,802
13	#7, #8 and #9 combined with upper 95% confidence limit for FAc recurrence free survival	£16,218

FAc - fluocinolone acetonide
* with hazards applied to fluocinolone acetonide arm post 36 months, also basis for all subsequent analyses

There are a number of limitations associated with the economic case.

- Alternative options that may be used in the treatment of active disease are not evaluated.
- The model addresses recurrence in a single eye, leading to uncertainty regarding the long-term prognosis for blindness and the appropriate incidence rates, and quality of life and resource assumptions.
- A key limitation is uncertainty regarding the estimation of recurrence rates where recurrence includes use of prohibited medications. As the clinical study tapers off use of medication this may contribute to the imputed recurrence, potentially, though not necessarily, more so in the control arm as patients are essentially untreated.
- There are uncertainties regarding the approach to application of health state utilities. These combine with uncertainty around the appropriate decrement for blindness and the foregoing issues regarding recurrence and rates of blindness.
- Whether the early sudden fall in recurrence-free survival for fluocinolone acetonide seen in the clinical study would apply in routine practice is unclear.

Despite the above uncertainties the economic case has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the Birdshot Uveitis Society and RNIB Scotland, both organisations are registered charities.

- Neither organisation has received any pharmaceutical company funding in the past two years.

- Recurrent non-infectious posterior (birdshot) uveitis is a rare, progressive and potentially blinding type of autoimmune non-infectious uveitis in the posterior segment of the eye. It has effects on all sight-related activities of daily living. Patients fear the possibility of blindness, not being able to continue to work or to drive, not being able to see children grow up, and losing their independence. Treatment is usually carried out in hospitals at uveitis clinics, often requiring frequent visits for patients to receive examinations, tests and monitoring.

- Current systemic treatments (oral and injectable medicines) can give rise to physical and mental side-effects. In addition, they may not always be effective or well tolerated. The benefits of the currently available intravitreal corticosteroid injections are relatively short-lasting.

- The longer duration of action of fluocinolone acetonide (Iluvien) intravitreal implant would mean fewer clinic attendances and fewer eye injections for patients, and a longer period of time until relapse of uveitis. The implant would also be particularly useful for patients who are

unable to take oral corticosteroids for treatment of disease flares. An increased risk of developing cataracts was noted.

Additional information: guidelines and protocols

There are no national guidelines for treatment of uveitis.

Additional information: comparators

No comparators specifically licensed for this indication.
Dexamethasone intravitreal implant may be used in patients with active disease (current inflammation in the eye) and worsening vision with a risk of blindness.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
fluocinolone acetonide	One intravitreal implant (190micrograms) to be administered into the affected eye.	5,500

Costs from BNF online on 8 March 2020. Each implant releases fluocinolone acetonide for up to 36 months. There are no data to support retreatment. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated that there would be 36 patients eligible for treatment with fluocinolone acetonide in year 1 and 166 patients in year 5. The estimated uptake rate was 100% in year 1 (36 patients) and 100% in year 5 (166 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

1. Alimera Sciences Limited. Fluocinolone acetonide (Iluvien®) 190 micrograms intravitreal implant in applicator. Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 28 March 2019.
2. Medicines and Healthcare products Regulatory Agency (MHRA). Public Assessment Report. Mutual Recognition Procedure. Fluocinolone Acetonide (Iluvien®) 190 micrograms Intravitreal Implant in Applicator. 22/03/2019 UK/H/3011/001/II/022 {www.products.mhra.gov.uk}.
3. Jaffe GJ, Foster, S., Pavesio, C. E., Paggiarino, D. A., Riedel, G. E. Effect of an Injectable Fluocinolone Acetonide Insert on Recurrence Rates in Chronic Noninfectious Uveitis Affecting the Posterior Segment: Twelve-Month Results. Ophthalmology. 2019;126(4):601-10.
4. EyePoint Pharmaceuticals Inc, PSV-FAI-001 month 36 clinical study report. 21 September 2018.
5. EyePoint Pharmaceticals Inc. Month 12 Clinical Study Report PSV-FAI-001. 17 February 2017.
6. Huang JJ., Elia M. Uveitis. BMJ Best Paractice. 28 March 2018. Available at www.bestpractice.bmj.com Last reviewed February 2020. [cited.
7. Dick A.D, Tundia N, Sorg R et al. Risk of Ocular Complications in Patients with Noninfectious Uveitis, Posterior Uveitis or Panuveitis. Ophthalmology 2016;123(3):655-662.
8. The Multicenter Uveitis Steroid Treatment Trial Follow-up Study Research Group, Kempten J.H., Altawee M.M., et al. Randomized Comparison of Systemic Anti-inflammatory Therapy Versus Fluocinolone Acetonide Implant for Intermediate, Posterior and Panuveitis: The Multicenter Uveitis Steroid Treatment Trial. Ophthalmology. 2011;118(10):1916-1926
9. Czoski-Murray C, Carlton K, BrazierJ, et al. Valuing Condition-Specific Health States Using Simulation Contact Lenses. Value in Health. 2009;12:793-799.
10. Adalimumab and dexamethasone for treating non-infectious uveitis. National Institute for Heath and Care Excellence (NICE). Technology appraisal guidance. TA460. July 2017.

This assessment is based on data submitted by the applicant company up to and including 17 July 2020.

**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*

Medicine 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 medicine 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

NHSScotland 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 NHSScotland 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.