CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

FLUOCINOLONE ACETONIDE (ILUVIEN — KNIGHT THERAPEUTICS INC.)
Indication: Diabetic macular edema

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that the fluocinolone acetonide intravitreal implant should not be reimbursed for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

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The CADTH Canadian Drug Expert Committee (CDEC) recommends that the fluocinolone acetonide intravitreal implant should not be reimbursed for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Reasons for the Recommendation

1. There was no direct evidence comparing fluocinolone acetonide intravitreal implant with other active treatments used in Canada for the treatment of adult patients with DME (e.g., laser therapy, intravitreal steroid, or anti-vascular endothelial growth factor [VEGF] therapies). The two phase III randomized controlled trials (RCTs) identified in the systematic review (FAME-A and FAME-B) were designed to compare fluocinolone acetonide with sham treatment.
2. Inconsistent results in measures of best-corrected visual acuity (BCVA) were observed within each FAME study and across the trials. In both trials, fluocinolone acetonide intravitreal implant with a daily release of 0.2 mcg demonstrated a modest treatment effect in the proportion of patients with an increase from baseline of 15 or more letters in BCVA compared with sham at month 24 (26.8% and 30.6% of patients in the fluocinolone acetonide 0.2 mcg/day group compared with 14.7% and 17.8% of patients in the sham group in FAME-A and FAME-B, respectively). However, no between-groups difference in the proportion of patients with a worsening from baseline of three or more steps in the Early Treatment Diabetic Retinopathy Study (ETDRS) multi-step eye scale of diabetic retinopathy was observed in either trial. Results of secondary outcomes were either not statistically significant or not consistent between trials.
3. In both trials, a higher percentage of patients in the fluocinolone acetonide 0.2 mcg/day group experienced ocular-related adverse events than in the sham group (cataracts [FAME-A: [redacted]% versus [redacted]%; FAME-B: [redacted]% versus [redacted]%], cataract operation [FAME-A: [redacted]% versus [redacted]%; FAME-B: [redacted]% versus [redacted]%]. Increased intraocular pressure was reported in a greater percentage of patients treated with fluocinolone acetonide than in sham-treated patients [FAME-A: [redacted]% versus [redacted]%; FAME-B: [redacted]% versus [redacted]%]). In phakic patients (i.e., those capable of developing cataracts) cataract development occurred in 82% of fluocinolone acetonide-treated patients and 50% of sham-treated patients in FAME-A and FAME-B combined. Cataract surgery was required in 80% of phakic fluocinolone acetonide-treated patients and 27% of sham-treated patients during the trials.
4. There are insufficient data to assess the safety and efficacy of fluocinolone acetonide in patients who would use fluocinolone acetonide intravitreal implant as a second-line therapy (e.g., have had an inadequate response to or did not tolerate prior anti-VEGF therapy). Anti-VEGF therapy is considered first-line treatment for DME in Canada, but responses of patients previously treated with anti-VEGFs to fluocinolone acetonide is unknown. The number of patients with prior exposure to anti-VEGF treatment (between 4.2% and 7.5%) was lower in the FAME trials than in Canadian clinical practice. In addition, patients enrolled in the FAME trials were not required to have been previously treated with a course of corticosteroids, as stipulated in the Health Canada indication.

Discussion Points

- CDEC noted that the potential benefits associated with less frequent dosing may not be realized due to the continued monitoring expected for all patients treated with fluocinolone acetonide intravitreal implant. According to the clinical expert consulted by CADTH, patients treated with a fluocinolone acetonide intravitreal implant would continue to require close ophthalmological follow-up over 36 months to evaluate potential harms regardless of the benefit to visual acuity.
- The Health Canada indication limits the treatment with a fluocinolone acetonide intravitreal implant to patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. CDEC considered that there may be various interpretations of the Health Canada indication for a fluocinolone acetonide implant in clinical practice, with respect to the dosage or duration of therapy of prior corticosteroids. CDEC was concerned about the implications of long-term exposure to intraocular corticosteroids in patients whose tolerability to a shorter course of corticosteroid treatment (in terms of intraocular pressure) has not been carefully assessed.

Background

Fluocinolone acetonide intravitreal implant has a Health Canada indication for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. Fluocinolone acetonide is a corticosteroid that acts to inhibit inflammatory responses to a variety of inciting drugs. It is available as a non-biodegradable intravitreal implant containing 0.19 mg fluocinolone acetonide designed to release 0.2 mcg fluocinolone acetonide per day for 36 months. The Health Canada–approved dose is one 0.19 mg intravitreal implant.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by the CADTH Common Drug Review: a systematic review of RCTs of the fluocinolone acetonide intravitreal implant, one indirect treatment comparison (ITC), and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered input from a clinical expert with experience in treating patients with DME, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Four patient groups including The International Federation on Ageing, The Canadian Council of the Blind, Diabetes Canada, and the Canadian Association for Retired Persons, jointly provided input for this submission. Patient perspectives were obtained from an online survey (N = 5) and telephone interviews (N = 4). The following is a summary of key input from the perspective of the patient groups:

- The patient groups' input indicated that blindness and vision loss are the most important aspects of the condition to control, along with vision impairment (e.g., blurry vision, floaters, or double-vision). Patients indicated that DME has an impact on their vision-related function (i.e., reading, driving, and housework), reduces their health-related quality of life, and increases their dependence on others. Other challenges reported included the lack of timely access to specialists, the travel distance and time required to receive treatment, and the out-of-pocket cost of treatment. Caregiver concerns included the need to take time off work to take patients to appointments and difficulty with administering treatment (e.g., swallowing pills).
- None of the patients who provided input reported currently receiving any other medications for the treatment of DME, although one patient surveyed had previously used both Lucentis and Avastin and at least two of those surveyed had prior experience with Lucentis.
- All five patients assessed using the online survey stated that it was "extremely important" to have longer-term vision improvement in a new treatment for DME. The four patients who had experience with Iluvien (all residents of the US) mentioned the following advantages of the treatment: the reduction in the number of injections (from every one to three months, to every two to three years), less worry about infections, elimination of swelling, less time off of work to attend appointments, and a decrease in discomfort due to less frequent injections.

Clinical Trials

The systematic review included FAME-A (N = 481) and FAME-B (N = 475). These trials were identically designed, multicenter, double-masked, sham-controlled, phase III RCTs that enrolled adult patients with DME who had at least one macular laser treatment more than 12 weeks before the screening visit. The primary objective of both trials was to determine if either dose level of the fluocinolone acetonide intravitreal implant (daily release rate of 0.2 mcg or 0.5 mcg) was superior to the control group with respect to the proportion of patients with a greater than or equal to 15-letter increase in BCVA at month 24 compared with baseline (primary end point). Patients were randomized in a 2:2:1 ratio to receive treatment with a 0.2 mcg/day fluocinolone acetonide implant, 0.5 mcg/day fluocinolone acetonide implant, or sham injection, respectively. The Health Canada-recommended dose of 0.2 mcg/day fluocinolone acetonide implant is the focus of this review.

Key limitations of the FAME trials included generalizability issues related to the baseline characteristics of the included patients (e.g., use of prior medications or laser treatments not consistent with the Canadian patient population), differential trial discontinuation, and the lack of evidence comparing fluocinolone acetonide 0.2 mcg/day with other treatments used for DME in Canada. Additionally, the considerable use of retreatments with the fluocinolone acetonide implant, including use of laser and use of disallowed treatments for DME, over the study period may confound the assessment of the treatment effect of the fluocinolone acetonide implant. In FAME-A

the proportion of patients that discontinued the trial was similar between the sham group ([redacted]%) and the fluocinolone acetonide 0.2 mcg/day group ([redacted]%). In FAME-B, more patients discontinued in the sham group ([redacted]%) compared with the fluocinolone acetonide 0.2 mcg/day group ([redacted]%). The most common reasons for discontinuation were attributed to loss to follow-up, withdrawal of consent, and death.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, CDEC discussed the following:

- BCVA: Visual acuity end points were assessed using ETDRS charts. ETDRS charts present a series of five letters of equal difficulty on each row with standardized spacing between letters and rows, for a total of 14 lines (70 letters). For macular edema, the FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with greater than or equal to 15-letter change in visual acuity, as clinically relevant outcome measures in trials of interventions.
- ETDRS multi-step eye scale of diabetic retinopathy: This validated scale was developed to categorize severity of diabetic retinopathy based on several fundus photographic characteristics and has become the reference standard for diabetic retinopathy grading in clinical trials. There are 13 levels in the original ETDRS scale and severity step or level increase is associated with an increased risk of retinopathy progression. The ETDRS Diabetic Retinopathy Severity Scale has a reported minimal clinically important difference (MCID) of two steps of progression at one-year follow-up. The FDA recommended the percentage of patients with a greater than or equal three-step change at three years on the ETDRS Diabetic Retinopathy Severity Scale as an outcome for diabetic retinopathy clinical trials.
- Vision Function Questionnaire (VFQ): Health-related quality of life (specific to vision-related function) was assessed using the 25-item Vision Function Questionnaire (VFQ-25) or the VFQ- 39 for English-speaking patients. The VFQ was developed to measure vision-targeted quality of life. The VFQ was reported to be a valid and reliable measure of health-related quality of life among patients with a wide range of eye conditions; however, recent studies have suggested that it may be more appropriately identified as a measure of visual functioning. The VFQ-25 has a reported MCID between 3.3 points and 6.13 points for the overall composite score. No validity information or MCID information on the VFQ-39 were identified from the literature.

Efficacy

According to the clinical expert consulted for this review, an improvement in visual acuity is key in determining a clinically meaningfully response to treatment in patients with DME; and this was echoed by the patient groups consulted for this review. The primary end point in the FAME trials was the difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA at month 24. This difference was statistically significantly in favour of treatment with fluocinolone acetonide 0.2 mcg/day group compared with the sham group in both trials (FAME-A: difference = –12.1%; 95% CI, –21.6 to –2.6, *P* = 0.029; FAME-B: difference = –12.9 %; 95% CI, –23.2 to –2.6, *P* = 0.030). The 15 or more letter criterion is consistent with recommendations from the FDA. Visual acuity was also assessed based on the mean change from baseline in BCVA letter score. Results were inconsistent between trials as only FAME-B was statistically significant in favour of fluocinolone acetonide 0.2 mcg/day compared with sham at month 24 (FAME-A: difference = –1.8 letters, 95% CI, –6.3 to 2.8, *P* value = 0.444; FAME-B: difference = –6.1 letters, 95% CI, –10.8 to –1.4, *P* = 0.011).

Findings from subgroup analyses may suggest that the treatment effect of fluocinolone acetonide 0.2 mcg/day on BCVA was more pronounced in patients with poorer visual acuity at baseline or patients who were pseudophakic. The differences in the proportion of patients with an increase from baseline of 15 or more letters in BCVA by baseline lens status were consistently greater in the pseudophakic subgroup compared with the phakic subgroup. However, further study is needed to confirm the effect due to the exploratory nature of the subgroup analyses.

Other outcomes identified in the CDR review protocol included the proportion of patients with a worsening from baseline of three or more steps in the ETDRS multi-step eye scale of diabetic retinopathy that did not show a difference between those treated with fluocinolone acetonide 0.2 mcg/day and those treated with sham (FAME-A: difference = [redacted]; 95% CI, [redacted], *P* value = [redacted]; FAME-B: difference = [redacted]; 95% CI, [redacted], *P* = [redacted]). In both FAME trials, the VFQ-39 change from baseline at month 24 was not different between treatment groups for fluocinolone acetonide 0.2 mcg/day compared and sham (FAME-A:

difference = [redacted]; 95% CI, [redacted]; FAME-B: difference = [redacted]; 95% CI, [redacted]). Similar results were reported for the VFQ-25. In the FAME trials, the VFQ-25 change from baseline at month 24 was not different between treatment groups for fluocinolone acetonide 0.2 mcg/day compared and sham (FAME-A: difference = [redacted]; 95% CI, [redacted]; FAME-B: difference [redacted]; 95% CI, [redacted]).

Harms (Safety)

Ocular adverse events (AEs) in the study eye occurred more frequently in the fluocinolone acetonide 0.2 mcg/day group in both trials. In FAME-A, [redacted]% of patients in the sham group and [redacted]% of patients in the fluocinolone acetonide 0.2 mcg/day group experienced an ocular AE in the study eye. Similarly, in FAME-B, [redacted]% of patients in the sham group and [redacted]% of patients in the fluocinolone acetonide 0.2 mcg/day group experienced an ocular AE in the study eye. The most common ocular AEs in the study eye were related to cataracts, cataract operation, and increased intraocular pressure, which affected more patients in the fluocinolone acetonide 0.2 mcg/day group than in the sham group in both trials.

Ocular serious adverse events (SAEs) in the study eye occurred more frequently in the fluocinolone acetonide 0.2 mcg/day group in both trials. In FAME-A, [redacted]% of patients in the sham group and [redacted]% of patients in the fluocinolone acetonide 0.2 mcg/day group experienced an ocular SAE in the study eye. In FAME-B, [redacted]% of patients in the sham group and [redacted]% of patients in the fluocinolone acetonide 0.2 mcg/day group experienced an ocular SAE in the study eye. The most common ocular SAEs in the study eye were related to cataract operations, which affected more patients in the fluocinolone acetonide 0.2 mcg/day group than in the sham group in both trials.

In both FAME trials the following notable harms were reported more often in patients in the fluocinolone acetonide 0.2 mcg/day group compared with the sham group: cataracts, endophthalmitis, eye infections, retinal tear, increased intraocular pressure, and glaucoma.

Indirect Treatment Comparisons

One manufacturer-supplied ITC was summarized and critically appraised in this CDR review. The primary aim of this ITC was to compare the clinical efficacy (visual acuity) and safety (cataract surgery, glaucoma) of the fluocinolone acetonide intravitreal implant to alternative treatments for DME by performing a Bayesian mixed treatment comparison of RCTs.

Based on the results of the submitted ITC, treatment with [redacted]

Limitations pertaining to heterogeneity of the population, inadequate reporting of baseline characteristics, differences in study designs, and sparse networks prevent any definitive conclusions from being made regarding the efficacy and safety of fluocinolone acetonide compared with other treatments for DME.

Cost and Cost-Effectiveness

The fluocinolone acetonide intravitreal implant is available as a non-biodegradable 0.19 mg intravitreal implant with a submitted price of $7,770. The recommended dosing schedule is one implant, which is designed to release fluocinolone acetonide over three years, at a rate of approximately 0.2 mcg/day.

The manufacturer submitted a cost-utility analysis (CUA) of patients with DME who had received at least one prior laser treatment, comparing fluocinolone acetonide implant with best supportive care (BSC; includes triamcinolone acetate, dexamethasone, bevacizumab, ranibizumab, and laser as concomitant therapies) to BSC alone from the perspective of a Canadian publicly funded health care payer during a 15-year time horizon. The CUA consisted of 14 health states that included 13 visual acuity health states based on best-corrected ETDRS letters of a treated eye, and an absorbing death state. FAME trial data were used to inform patient

transitions between health states every three months. The manufacturer assumed an increased risk of mortality in patients with diabetes and DME compared with the general population.

It was assumed that patients responding to fluocinolone acetonide implant (defined as a ≥ 15 ETDRS-letter improvement over three years) could be retreated every three years. All other patients were assumed to not receive further treatment. Health-related quality of life utility values were sourced from a study of US patients with age-related macular degeneration. Direct medical costs included the costs of drugs, health care resource use, and blindness.

In the manufacturer's probabilistic base-case analysis, fluocinolone acetonide implant plus BSC was associated with an incremental cost-utility ratio (ICUR) of $72,853 per quality-adjusted life-year (QALY) gained. At a willingness-to-pay threshold of $50,000 per QALY, the fluocinolone acetonide implant plus BSC had a 16% probability of being cost-effective compared with BSC alone.

CADTH identified the following key limitations:

- The manufacturer inappropriately used a blended mix of comparators that constituted BSC in both the intervention and comparator groups and did not allow the cost-effectiveness of fluocinolone acetonide implant to be assessed against individual comparators.
- It is uncertain whether key clinical inputs, some of which were outdated, are generalizable to the Canadian population:
    - Many patients included in the FAME trials had prior laser therapy, while the Health Canada indication specifies prior corticosteroid treatment.
    - According to the clinical expert consulted by CADTH, a greater proportion of the Health Canada-indicated population would have previously tried intravitreal anti-VEGF treatments than observed in the FAME trials.
- The manufacturer used health utility data that were elicited using an unvalidated approach in a population with unclear relevance to DME. The manufacturer also made two inappropriate assumptions: changes in worse-seeing eye visual acuity were assumed to have the same impact on quality of life as changes in better-seeing eye visual acuity; and patients treated bilaterally were assumed to experience a 25% gain in health utility.
- Costs of fluocinolone acetonide implant retreatments within the first three years, as observed in FAME trials, were not captured and the cost of blindness was inappropriately applied to patients who were not legally blind. These assumptions favoured fluocinolone acetonide implant.

The CADTH reanalysis incorporated Canadian mortality and cost of blindness data, applied cost of blindness only to patients with visual acuity below 35 ETDRS letters, applied the cost of fluocinolone acetonide implant retreatment, and addressed limitations associated with health utility data source and assumptions.

In the CADTH base case, the ICUR was $91,452 per QALY gained for fluocinolone acetonide implant plus BSC versus BSC alone. At a willingness-to-pay threshold of $50,000 per QALY, fluocinolone acetonide implant plus BSC was associated with 4% probability of being the optimal intervention. A price reduction of more than 45% is required to achieve an ICUR less than $50,000 per QALY. There remains notable uncertainty associated with the cost-effectiveness of the fluocinolone acetonide intravitreal implant as there were limitations with the model structure, data sources, and uncertainty associated with the extrapolation of long-term costs and consequences that could not be addressed by CADTH.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

August 21, 2019 Meeting

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None