CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Fluocinolone acetonide intravitreal implant (Iluvien)

(Knight Therapeutics Inc.)

Indication: 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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Abbreviations

AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
BSC	best supportive care
BSE	better-seeing eye
CUA	cost-utility analysis
DME	diabetic macular edema
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluocinolone acetonide
HRQoL	**health-related quality of life**
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year
VEGF	vascular endothelial growth factor
WSE	worse-seeing eye

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Fluocinolone acetonide (FA) intravitreal implant (Iluvien)
Study Question	To assess the cost-effectiveness of the FA intravitreal implant compared with best supportive care (BSC)[a] in patients with diabetic macular edema (DME) who received at least one prior therapy.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with DME who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.
Treatment	0.19 mg FA intravitreal implant plus BSC[a]
Outcome	Quality-adjusted life-year (QALY)
Comparator	BSC[a]
Perspective	Canadian public health care payer
Time Horizon	15 years
Results for Base Case	ICUR = $72,853 per QALY gained compared with BSC.

Key Limitations	• The manufacturer inappropriately used a blended mix of comparators that did not allow the cost-effectiveness of the FA implant to be assessed against individual comparators.
	• It is uncertain whether key clinical inputs are generalizable to the Canadian population:
	  ○ The patients included in the FAME trials mostly had a prior laser treatment, while the Health Canada (HC) indication specifies a prior corticosteroid treatment.
	  ○ According to the clinical expert consulted by CADTH, a greater proportion of the HC-indicated population would have previously tried intravitreal anti–vascular endothelial growth factor (VEGF) treatments than was observed in the FAME trials.
	  ○ The mix of concomitant treatments in the FAME trials does not reflect Canadian clinical practice as aflibercept, a key anti-VEGF treatment, was not included.
	  ○ A mix of international and outdated evidence was used to inform mortality and adverse event inputs in the model.
	• There was insufficient evidence for CADTH clinical reviewers to determine the comparative efficacy and safety of the FA implant compared with other treatments for DME (i.e., anti-VEGFs, corticosteroids, and laser therapy).
	• The manufacturer used health-utility data that was elicited using an unvalidated approach in a population with unclear relevance to DME. The manufacturer also made two inappropriate assumptions: the change in WSE visual acuity was assumed to have the same impact on quality of life as a change in BSE visual acuity, and patients treated bilaterally were assumed to experience a 25% gain in health utility.
	• The manufacturer underestimated the costs associated with FA implant plus BSC treatment. Costs of FA implant re-treatments within the first three years, as observed in the FAME trials, were not captured and the cost of blindness was inappropriately applied to patients who were not legally blind. These assumptions favoured FA implants.
	• The manufacturer's modelling approach did not comprehensively capture the uncertainty associated with long-term costs and consequences.

CADTH Estimates	
	• 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 and who had received FA implant re-treatment, 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 FA implant plus BSC versus BSC alone. At a willingness to pay of $50,000 per QALY, FA implant plus BSC was associated with a 4% probability of being the optimal intervention. A price reduction of more than 45% is required to achieve an ICUR of less than $50,000 per QALY. • CADTH could not address the remaining limitations associated with model structure, data sources, and uncertainty associated with the extrapolation of long-term costs and consequences. Consequently, several subgroup analyses and scenario analyses were explored. In these analyses, the ICUR for FA implant plus BSC compared with BSC alone ranged between $72,069 and $177,495 per QALY gained.

BSC = best supportive care; BSE = better-seeing eye; DME = diabetic macular edema; FA = fluocinolone acetonide; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; WTP = willingness to pay; WSE = worse-seeing eye.

[a] BSC was defined as the mix of concomitant therapies observed in the FAME trials, such as triamcinolone acetate, dexamethasone, bevacizumab, ranibizumab, and laser therapy. Non-laser therapies were considered off-protocol.

Drug	Fluocinolone acetonide (Iluvien)
Indication	For the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.
Reimbursement Request	As per indication.
Dosage Form(s)	Sterile intravitreal implant, 0.19 mg
NOC Date	November 23, 2018
Manufacturer	Knight Therapeutics Inc.

Executive Summary

Background

Fluocinolone acetonide (FA) intravitreal implant (Iluvien), a corticosteroid, is indicated 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.[1] Iluvien is a non-biodegradable 0.19 mg intravitreal implant with a submitted price of $7,770 per implant. The recommended dosing schedule is one implant, which is designed to release FA over three years at a rate of approximately 0.2 mcg per day.[2] FA implant was previously reviewed by CADTH in 2018. The manufacturer, however, chose to withdraw the submission during the review period.[3]

The manufacturer submitted a cost-utility analysis (CUA) that modelled patients with DME who had received at least one prior laser treatment as per the three-year FAME trials.[4] The CUA compared FA implant plus best supportive care (BSC) with BSC alone from the perspective of a Canadian publicly funded health care payer, and discounted both costs and quality-adjusted life-years (QALYs) at a rate of 1.5% per annum over a 15-year time horizon. BSC included the use of concomitant therapies (triamcinolone acetate, dexamethasone, bevacizumab, ranibizumab, and laser therapy). The proportion of patients receiving each concomitant therapy was determined by their use in the FAME trials. Based on input from Canadian clinicians, 70% of patients were assumed to be treated unilaterally, and 30% of patients were assumed to be treated in both eyes.

The CUA consisted of 14 health states that included 13 visual acuity health states based on the best-corrected visual acuity (number of Early Treatment Diabetic Retinopathy Study [ETDRS] letters) of a treated eye (better-seeing eye [BSE] was tracked for bilaterally treated patients) and an absorbing death state. Patients entered the model based on the distribution of patients across the visual acuity health states observed in the FAME trials[5,6] and could transition every three months to different health states based on the efficacy inputs from the FAME trials. Mortality rates in the model considered the increased risk of mortality in patients with diabetes and DME compared with the general UK population.[4] It was assumed that patients responding to FA implant (defined as an improvement of ≥ 15 ETDRS letters over three years) could be re-treated every three years. All other patients were assumed to not receive any further treatment.

Adverse events were modelled using rates from the FAME trials and US observational studies.[7,8] Health-related quality of life (HRQoL) utility values were sourced from a study of US patients with age-related macular degeneration (AMD).[9] The manufacturer assumed that health utilities would have the same relationship to worse-seeing eye (WSE) visual acuity as for BSE visual acuity in patients who were unilaterally treated in the BSE, and that there would be a 25% utility gain associated with bilateral treatment.

Direct medical costs were estimated using Canadian sources, except for the cost of blindness, which was based on a US study.[4] The cost of blindness (attributable to non–eye-related medical costs [e.g., falls, depression, and long-term care]) was applied to patients with BSE visual acuity below 65 ETDRS letters.

In the manufacturer's probabilistic base-case analysis, FA implant plus BSC was associated with 0.16 additional QALYs and an additional cost of $11,625 compared with BSC alone, resulting in an incremental cost-utility ratio (ICUR) of $72,853 per QALY gained. At a willingness-to-pay threshold of $50,000 per QALY, FA implant plus BSC had a 16% probability of being cost-effective compared with BSC alone.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the manufacturer's economic evaluation.

The manufacturer inappropriately used a blended mix of treatments to represent BSC, which did not allow the cost-effectiveness of the FA implant to be assessed against individual comparators.

It is uncertain whether the clinical evidence in the submitted model would be reflective of a Canadian population and treatment practice. The FAME trials reflected a population that had prior laser therapy instead of previous treatment with a course of corticosteroids, as per the Health Canada indication. The trial population also had less prior experience with anti–vascular endothelial growth factor (VEGF) therapy than would be expected by the clinical expert consulted by CADTH. General mortality data were sourced from the UK, and some mortality and adverse event inputs were obtained from outdated sources from the US that may not reflect the current experience of Canadian patients with diabetes.

The manufacturer's approach to modelling clinical effects and the evidence underlying this approach were associated with uncertainty. There was insufficient evidence for CADTH clinical reviewers to determine the comparative efficacy and safety of FA implant compared with other treatments for DME (including anti-VEGFs, corticosteroids, and laser therapy). Evidence from the FAME trials was limited due to the confounding effect of re-treatment and concomitant therapies, safety concerns, and uncertain generalizability to the Canadian population, whereas the manufacturer-submitted indirect treatment comparison was limited due to the heterogeneity of the patient population, study design, and sparse network of evidence.

In addition, the manufacturer used health-utility data that was elicited using an unvalidated approach in a population with unclear relevance to DME (i.e., patients with AMD with an unknown proportion of diabetic retinopathy and DME). The manufacturer also made two inappropriate assumptions that were contradicted by the submitted literature and the clinical expert consulted by CADTH: changes in WSE visual acuity were assumed to have the same impact on quality of life as changes in BSE visual acuity, and bilaterally treated patients were assumed to experience a 25% gain in health utility. Costs were also inappropriately

modelled and likely underestimated the costs associated with FA implant plus BSC treatment. Costs of FA implant re-treatment, as observed in the FAME trials within the first three years, were not captured, and the cost of blindness was inappropriately applied to patients with visual acuity below 65 ETDRS letters (35 ETDRS letters, equivalent to 20/200 vision, signifies the threshold for legal blindness[10]). The modelling of costs favoured FA implants.

The manufacturer's modelling approach did not allow for probabilistic exploration of key parameters, nor did it comprehensively capture the uncertainty associated with long-term costs and consequences. This, combined with data source limitations and uncertain long-term expected use of FA implants, mean the results from the model must be interpreted with caution.

CADTH's reanalysis, which incorporated Canadian mortality and cost-of-blindness data, applied the cost of blindness only to patients with visual acuity below 35 ETDRS letters, incorporated the cost of FA implant re-treatment, and addressed the limitations associated with the health utility data source and assumptions. In the CADTH base case, the ICUR was $91,452 per QALY gained for FA implant plus BSC versus BSC alone. At a willingness to pay of $50,000 per QALY, FA implant plus BSC was associated with a 4% probability of being the optimal intervention. A price reduction of more than 45% is required to achieve an ICUR of less than $50,000 per QALY. CADTH could not address the remaining limitations associated with model structure, data sources, and uncertainty associated with the extrapolation of long-term costs and consequences. Consequently, several subgroup analyses and scenario analyses were explored. In those analyses, the ICUR for FA implant plus BSC compared with BSC alone ranged between $72,069 and $177,495 per QALY gained.

Conclusions

CADTH identified several key limitations with the manufacturer's model. Given the parameters that CADTH could modify in the manufacturer's model, CADTH's reanalysis estimated that the ICUR of FA implant plus BSC compared with BSC alone was $91,452 per QALY. At a willingness to pay of $50,000 per QALY, FA implant plus BSC was associated with a 4% probability of being cost-effective compared with BSC alone. A price reduction of more than 45% is required for FA implant plus BSC to achieve an ICUR of less than $50,000 per QALY compared with BSC alone.

However, given the limitations with the model structure, data sources, and uncertainty associated with the extrapolation of long-term costs and consequences that could not be adequately addressed in the CADTH reanalyses, caution should be applied in interpreting the cost-effectiveness results. Several subgroup analyses and scenario analyses were conducted to capture some of the uncertainties, and the ICURs in these analyses ranged between $72,069 per QALY gained and $177,495 per QALY gained.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted a cost-utility analysis (CUA) comparing treatment with fluocinolone acetonide (FA) intravitreal implant plus best supportive care (BSC) with BSC alone in patients (mean age 63.4 years) with diabetic macular edema (DME) who had received at least one prior laser treatment, as per the FAME registration trials.[4] BSC included the use of concomitant therapies such as triamcinolone acetate, dexamethasone, bevacizumab, ranibizumab, and laser therapy. The proportion of patients who received each concomitant therapy was derived using data from each treatment arm of the FAME trials. The CUA was conducted from the perspective of a Canadian publicly funded health care payer, and costs and quality-adjusted life-years (QALYs) discounted at a rate of 1.5% per annum over a 15-year time horizon. Based on the manufacturer's consultation with three Canadian clinical experts, 21% of patients were assumed to be treated unilaterally in the better-seeing eye (BSE), 49% unilaterally in the worse-seeing eye (WSE), and 30% bilaterally. For the patient cohort that received FA implant plus BSC, 70% of the bilaterally treated patients were assumed to receive FA implant plus BSC in both eyes, while the remaining 30% were assumed to receive FA implant plus BSC in one eye, and BSC alone in the other eye.

The CUA was structured as a Markov cohort state transition model and consisted of 14 health states: 13 visual acuity health states based on the number of Early Treatment Diabetic Retinopathy Study (ETDRS) letters of a treated eye (only BSE was tracked for bilaterally treated patients) and an absorbing death state (Figure 1). Patients entered the model as per the baseline distribution of visual acuity health states observed in each arm of the FAME trials. In the trials, patients who received FA implant and BSC had a mean baseline best-corrected visual acuity (BCVA) of approximately 53 letters, and patients who received BSC only had a mean baseline BCVA of approximately 55 letters. Costs and consequences were modelled as three-month cycles and, for the first three years, patients transitioned between visual acuity health states according to treatment based on the quarterly reported BCVA outcomes from the FAME trials. Beyond the first three years in the model, responders (defined as an improvement of ≥ 15 ETDRS letters over 36 months) in the FA implant plus BSC treatment group were assumed to receive ongoing FA implant re-treatment (without BSC) and were assumed to discontinue FA implant treatment based on rates reported in the FAME trials. Patients who did not respond to FA implant or who had received only BSC in the first three years were not assumed to receive any further treatment. Health-state transitions beyond the first three years differed according to treatment and were predicted using the last 12 months of observations from the FAME trials. The truncated data were used instead of the full data set in an attempt to minimize potential bias due to cataract surgeries occurring within the first two years of the trials.[4]

Adverse events (i.e., elevated intraocular pressure, cataract surgery, glaucoma procedure, vitrectomy, endophthalmitis, and retinal detachment) were modelled as observed in the FAME trials. However, some adverse events were not considered beyond three years in the model. Cataract and glaucoma were assumed to occur beyond the first three years in the model and their event rates were based on US observational studies.[7,8] Endophthalmitis and retinal detachment were assumed to only occur in patients who receive FA implant beyond the first three years in the model. Mortality was also modelled independently of treatment

and reflected the general UK population and the increased mortality risk of patients with diabetes and clinically significant macular edema compared with the general population.[4]

Health utilities for the BSE visual acuity health states in the model for unilaterally treated patients were based on time-trade-off utility values elicited from a study of US patients with age-related macular degeneration (AMD).[9] The manufacturer assumed that health utilities would have the same relationship to WSE visual acuity as for BSE visual acuity in patients who were unilaterally treated in the BSE. The manufacturer also assumed a 25% utility gain in bilaterally treated patients to account for the incremental utility benefit of treating WSE in addition to BSE. This was based on the manufacturer's interpretation of an observation of health-related quality of life (HRQoL) results in European patients with AMD.[11] Health-utility decrements associated with adverse events were not modelled.

Direct medical costs, including drug acquisition, administration, monitoring, and adverse event treatment costs were included. Associated resource utilization was informed by the manufacturer's consultation with Canadian clinicians, and unit costs were informed by provincial formularies and the Ontario Schedule of Benefits. The cost of blindness, representing direct medical costs attributable to non–eye-related costs (e.g., falls, depression, and long-term care), was based on a US Medicare claims data study[12,13] and was applied to patients if their BSE visual acuity dropped below 65 ETDRS letters.

Manufacturer's Base Case

The manufacturer's base-case probabilistic results are presented in Table 2. FA implant plus BSC was associated with 0.16 incremental QALYs at an additional cost of $11,625 compared with BSC alone, resulting in an incremental cost-utility ratio (ICUR) of $72,853 per QALY gained. At a willingness-to-pay threshold of $50,000 per QALY, FA implant plus BSC had a 16% probability of being cost-effective compared with BSC alone.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	Incremental Cost per QALY ($)
BSC	22,092		7.55		
FA implant + BSC	33,717	11,625	7.71	0.16	72,853

BSC = best supportive care; FA = fluocinolone acetonide; QALY = quality-adjusted life-year.

Source: Derived from the manufacturer's pharmacoeconomic submission[4] that was corrected by CADTH. The manufacturer had submitted a model with an error that did not use the last 12 months of the FAME trials to extrapolate transition probabilities for the cohort of patients treated with BSC alone.

Summary of Manufacturer's Sensitivity Analyses

Parameter uncertainty was addressed by probabilistic analysis while methodological and structural uncertainties were addressed by deterministic scenario analyses. Based on the manufacturer's sensitivity analyses of key assumptions, the results of the pharmacoeconomic model were found to be most sensitive to a shorter time horizon, alternative health-state utility values, and the exclusion of the cost of blindness.

Limitations of Manufacturer's Submission

The following limitations were identified with the manufacturer's pharmacoeconomic submission:

- **Inappropriate choice of comparator:** The manufacturer submitted a comparison of FA implant plus BSC compared with BSC alone. BSC was represented as a blended comparator (i.e., mix of multiple treatments) as used in the FAME trials. This mix of treatments does not reflect Canadian practice as aflibercept, a key anti–vascular endothelial growth factor (VEGF) treatment, was not included. Furthermore, the choice of a blended comparator is inappropriate, as it cannot provide information on the cost-effectiveness of FA implant relative to individual comparators of interest. Where there are multiple relevant comparators, the treatments should be considered on their own, and all comparators should be assessed in a sequential analysis. Although there was insufficient evidence for CADTH clinical reviewers to determine the comparative efficacy and safety of FA implant compared with other treatments for DME (including anti-VEGFs, corticosteroids, and laser), the manufacturer could have conducted a CUA of multiple comparators using the submitted indirect treatment comparison (ITC) and captured the associated uncertainty using probabilistic analysis. In lieu of such analysis, the cost-effectiveness of FA implant compared with other treatments, which may be of interest for decision-making, is unknown.
- **Key clinical inputs may not reflect the Canadian population:** It is uncertain whether the population presented in the FAME trials, the key clinical evidence used in the submitted CUA, reflects the Health Canada–indication population. Firstly, the patients included in the FAME trials mostly received previous treatment with laser therapy, while the Health Canada indication specifies prior treatment with a corticosteroid. According to the clinical expert consulted by CADTH, a greater proportion of patients who are likely to use FA implant would have previously tried intravitreal anti-VEGF treatments than was observed in the FAME trials. The manufacturer also used clinical inputs that may not be reflective of Canadian patients. Mortality risk was estimated using UK general mortality data and adjusted for potential increased risk due to DME based on UK[14] and US[15] literature. The studies were also based on a cohort of patients recruited in the early 1980s and 1990s[14,15] and may not reflect the mortality risk in Canadian patients with DME today, considering advances in diabetes management. The incidence of glaucoma and cataract surgeries beyond the first three years of the model was also based on US studies[7,8] that recruited patients in the early 1980s. Collectively, these limitations add uncertainty to the clinical outcomes reported in the submitted model. CADTH could not explore these limitations in the reanalyses due to the limitations of the manufacturer's data source and modelling approach.
- **Uncertain clinical efficacy in the target population:** The comparative clinical evidence for FA implant is unclear. Although a larger proportion of patients treated with FA implant showed clinically meaningful improvement (i.e., increase from baseline of ≥ 15 ETDRS letters) at month 24 compared with sham treatment in the FAME trials, the CADTH clinical reviewers were uncertain whether available clinical evidence showed clinically meaningful improvement in other vision-related outcomes. FA implant re-treatments and concomitant therapies in the FAME trials are potential confounders for the assessment of the treatment effect. The FA implant was deemed to have an unfavourable safety profile compared with sham injection (notably, more cataracts and increased intraocular pressure), and the generalizability of the evidence to the Canadian population was of concern. The comparative evidence from the manufacturer's ITC was also uncertain due

to the heterogeneity of the patient population, study design, and sparse network. The manufacturer's application of the FAME trial data in the submitted model further added uncertainty to the model results. The movement of patients across visual acuity health states over the first three years was based on a series of treatment-dependent distributions of patients rather than the standard modelling approach that uses transition probabilities and relative risks. The manufacturer's approach was also modelled deterministically and did not allow the reviewers to capture the uncertainty associated with the clinical efficacy parameters.

- **Uncertain quality-of-life benefit in the target population:** There is also uncertainty associated with the manufacturer's approach to translating visual acuity change to HRQoL benefit. The health-utility values used in the submitted model were derived from a population with AMD with an unknown proportion of diabetic retinopathy or DME,[9] and the clinical relevance to the DME population is unclear. The manufacturer also did not vary utility parameters probabilistically and the uncertainty associated with the utility values was not captured in the submitted model. Furthermore, the manufacturer assumed that changes in WSE visual acuity have the same impact on HRQoL as changes in BSE visual acuity, and that there is an additional 25% utility gain associated with visual acuity improvement in bilateral treatment.[4] Both assumptions were contradicted by the clinical expert consulted by CADTH and by studies cited by the manufacturer that report WSE visual acuity has little impact on HRQoL.[11,16] Collectively, these limitations add further uncertainty to the clinical outcomes and the associated HRQoL benefit attributable to FA implant reported in the manufacturer's pharmacoeconomic submission.
- **DME management costs are inappropriately captured:** Approximately 24% of patients who received FA implant (0.2 mcg per day) in the FAME trials received multiple doses within the first three years.[4] Costs associated with these re-treatments were not included in the submitted model and underestimate the total health care costs associated with FA implant treatment. The manufacturer also applied cost of blindness (associated with non–vision-related costs such as falls, depression, and long-term care stay) to patients whose BSE visual acuity fell below 65 ETDRS letters. This does not correspond to the definition of legal blindness of 20/200 vision[10] (which corresponds to 35 ETDRS letters). Consequently, the manufacturer overestimates cost savings associated with the potential prevention of blindness. It would be more appropriate to apply these costs only to patients whose BSE visual acuity falls below 35 ETDRS letters. Collectively, these two limitations underestimate the ICUR associated with FA implant compared with BSC.

  Lastly, the cost of blindness was sourced from a 2014 US study of Medicare claims from 1999 to 2003[12,13] and was inflated to 2018 Canadian dollars. It is inappropriate to apply these costs to Canadian patients when Canadian estimates are available from the literature.[17,18] The impact of using Canadian cost estimates was explored in the CADTH reanalysis (Table 3).
- **Long-term costs and consequences captured in the model are uncertain:** The validity of the manufacturer's model with a 15-year time horizon is uncertain due to the limited clinical evidence, uncertain potential for re-treatment, and lack of consideration of appropriate comparators and adverse events. As discussed in the CADTH Clinical Review report, the FAME trials were designed to assess the end points at month 24, although data were collected up to month 36. Consequently, the validity of the modelled clinical efficacy and safety based on the data between the second and third years of the trial is uncertain. As the manufacturer used trial data from this period to extrapolate efficacy beyond three years, the validity of economic outcomes over the extrapolated

period is also uncertain. Furthermore, there is additional uncertainty associated with the validity of this extrapolation due to the assumption that the uncertain efficacy and safety observed during the last year of the FAME trials would be consistently observed over the rest of the 15-year time horizon. According to the clinical expert consulted by CADTH for this review, the long-term visual acuity efficacy associated with continued corticosteroid treatment is uncertain. Despite the extent of uncertainty associated with the extrapolation based on the FAME trials, the manufacturer did not test assumptions regarding treatment efficacy plateauing or waning.

The manufacturer's model also assumed that patients with a response to FA implant will continue FA implant after three years. Given that there is only limited information on re-treatment after three years with FA implant and that the possible impact of implant residuals after injection is unknown,[2] the validity of this assumption is uncertain. The manufacturer also assumed that BSC treatments are stopped in all patients regardless of response after three years. According to a clinician consulted by CADTH, this is not an appropriate assumption. Furthermore, it was inappropriately assumed that adverse events, except for glaucoma and cataracts, do not occur after the first three years in patients treated with BSC.

In order to address the significant uncertainty associated with the modelling of long-term costs and consequences noted previously, CADTH explored shorter time horizons in its scenario analyses (10 years, five years, and three years).

CADTH Common Drug Review Reanalyses

To address several of the identified limitations, CADTH conducted the following reanalyses:

1. General population mortality was modelled based on Canadian life tables from Statistics Canada.[19]
2. Efficacy data from month 3 to month 36 of the FAME trials were used to extrapolate transition probabilities beyond the first three years of the model.
3. The cost of blindness was only applied below 35 ETDRS letters, the legal definition of blindness.[10]
4. A Canadian source for the cost of blindness was used instead of the US source.[13]
5. The cost was estimated to be $5,378 (compared with $4,997 in the manufacturer's base case). The cost was taken from an international cross-section study that reported Canadian population findings[18] and inflated to 2018 Canadian dollars using the Consumer Price Index.[20,21] The mean annual direct non–vision-related medical costs and the mean annual direct non-medical costs were considered. The costs from Canadian patients without neovascular AMD were subtracted from corresponding costs for patients who had neovascular AMD and severe vision loss. As community care and assistance for activities of daily living in Canada are funded both publicly and privately, only 52% of non-medical costs were considered to be funded publicly based on Statistics Canada's estimate of publicly funded home care.[22]
6. The number of FA implant administrations was increased by 24%, corresponding to the proportion of re-treatments in the FAME trial (18.7% of patients had a second dose and 5.3% had a third dose within three years).[4] This 24% increase in administrations was also assumed for the extrapolated periods in the model (i.e., year 4 to year 15).
7. Health utilities associated with visual acuity in the unilaterally treated BSE and WSE were sourced from the Health Utility Index Mark 3 values reported in the Heintz et al., 2012 study[16] (Table 13, Appendix 4). The utility values were varied probabilistically

between the reported 95% confidence intervals using the beta distribution. The 25% utility gain associated with bilateral treatment was also removed from the model.

The CADTH base case considered a combination of the reanalyses: 1, 3, 4, 5, and 6.

Compared with the manufacturer's results, the CADTH base-case analysis suggests fewer QALYs and more costs for the FA implant plus BSC compared with BSC alone (Table 3). At a willingness-to-pay threshold of $50,000 per QALY, FA implant plus BSC had a 4% probability of being cost-effective. Compared with BSC alone, the price of FA implant would need to be reduced by more than 45% for FA implant plus BSC to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.

Table 3: CADTH Reanalysis (Fluocinolone Acetate Implant Plus Best Supportive Care Versus Best Supportive Care Alone)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
	Manufacturer's base case[a]	FA implant + BSC	33,717	7.73	–
		BSC	22,092	7.55	–
		Incremental	11,625	0.16	72,853
1	Canadian mortality data	FA implant + BSC	42,189	9.96	–
		BSC	30,723	9,75	–
		Incremental	11,466	0.21	55,110
2	Transition probabilities for years 4 to 15 based on months 3 to 36 of FAME trials	FA implant + BSC	34,038	7.60	–
		BSC	22,536	7.45	–
		Incremental	11,502	0.16	73,825
3	Cost of blindness applied below 35 ETDRS letters	FA implant + BSC	27,616	7.73	–
		BSC	13,928	7.57	–
		Incremental	13,688	0.17	82,896
4	Canadian cost of blindness	FA implant + BSC	36,238	7.73	–
		BSC	25,360	7.57	–
		Incremental	10,878	0.17	65,878
5	24% increase in FA implant administrations	FA implant + BSC	37,056	7.73	–
		BSC	22,035	7.57	–
		Incremental	15,021	0.17	90,963
6	Probabilistic health-state utility values from Heintz et al., 2012[16]; no bilateral treatment utility benefit	FA implant + BSC	33,669	6.79	–
		BSC	22,035	6.63	–
		Incremental	11,634	0.16	72,500
CADTH Base Case					
	Reanalyses 1, 3, 4, 5, and 6	**FA implant + BSC**	**36,899**	**8.75**	–
		BSC	**18,539**	**8.55**	–
		Incremental	**18,360**	**0.20**	**91,452**

BSC = best supportive care; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Derived from the manufacturer's pharmacoeconomic submission that was corrected by CADTH. The manufacturer had submitted a model with an error that did not use the last 12 months of the FAME trials to extrapolate transition probabilities for the cohort of patients treated with BSC alone.

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICURs ($/QALY Gained) of FA Implant Plus BSC Versus BSC Alone		
Price	**Base-Case Analysis Submitted by Manufacturer[a]**	**Reanalysis by CDR**
Submitted	72,853	91,452
10% reduction	64,144	84,162
15% reduction	59,790	79,395
20% reduction	55,435	74,629
25% reduction	51,081	69,862
27% reduction	**49,339**	67,956
30% reduction	46,727	65,096
40% reduction	38,018	55,563
45% reduction	33,663	50,796
46% reduction	32,792	**49,843**

BSC = best supportive care; FA = fluocinolone acetonide; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Derived from the manufacturer's pharmacoeconomic submission that was corrected by CADTH. The manufacturer had submitted a model with an error that did not use the last 12 months of FAME trials to extrapolate transition probabilities for the cohort of patients treated with BSC alone.

Due to the uncertainties associated with the expert-elicited estimates regarding the proportions of unilaterally and bilaterally treated patients, the following four subgroup analyses were conducted (Table 14, Appendix 4):

S1a. Unilaterally treated in the BSE

S1b. Unilaterally treated in the WSE

S1c. Bilaterally treated (70% of those treated bilaterally received FA implant plus BSC in both eyes, 30% of those treated bilaterally received FA implant plus BSC in one eye and BSC alone in the other eye)

S1d. Bilaterally treated (all patients in the FA implant plus BSC group received FA implant plus BSC in both eyes)

International health technology assessment agencies have assessed FA implant for the treatment of DME in the subgroup of patients with a pseudophakic lens and at least three years of DME history[23-25] (Appendix 3). Given this context, CADTH conducted an exploratory subgroup analysis in this population using the FAME trial data that was included in the submitted model (subgroup analysis S2). Subgroup data were used to update model parameters associated with change in BCVA in the first three years, response rates, discontinuation rates, and adverse event probabilities. Of note, the manufacturer used a different response criterion for the pseudophakic chronic DME subgroup (improvement of ≥ 10 ETDRS letters over three years) than the manufacturer's base case (improvement of ≥ 15 ETDRS letters over three years).[4] As cataracts are not key adverse events in the pseudophakic population, efficacy was also extrapolated based on the last 30 months of the FAME trials (as conducted for the National Institute for Health and Care Excellence[26] and Scottish Medicines Consortium[25]), which is broader than the last 12 months of data from the FAME trials that were used in the manufacturer's base case. The results of this exploratory subgroup analysis should be interpreted with caution due to the statistical limitations associated with the exploratory nature of the pseudophakic subgroup end points from FAME trials.

Furthermore, given substantial uncertainties associated with long-term extrapolation, time horizons of 10, five, and three years (which correspond to the duration of the FAME trials) were explored as scenario analyses (subgroup analysis S3a, S3b, and S3c).

Subgroup analyses and scenario analyses are presented in Table 14, Appendix 4. In these analyses, the ICUR for FA implant plus BSC compared with BSC alone ranged between $72,069 and $177,495 per QALY gained.

Issues for Consideration

Compared with other intravitreal corticosteroid injections that require multiple annual injections, FA implants are reported to last for three years. The longer duration of efficacy would be more convenient for rural patients, as they might not need to travel as frequently to manage DME. However, there is a lack of evidence regarding the removal of the FA implant from the treated eye[2] for those who experience adverse events or do not respond.

Patient Input

Input was received jointly from four patient groups: The International Federation on Ageing, the Canadian Council of the Blind, Diabetes Canada, and the Canadian Association for Retired Persons. Seven patients with DME and two caregivers provided input. Four of the patients were from the US, one respondent was from Australia, and the rest of the respondents were from Canada. None of the patients were receiving medications for the treatment of DME at the time of feedback; four US patients had experienced a single Iluvien dose and one patient had previous experience with anti-VEGF medications.

The respondents explained that attending medical appointments for DME, the need to rely on others, and isolation most significantly impact their life. Although the patients ranked blindness and vision loss as the most important aspect of concern, others reported challenges included travel time and distance getting to treatment, cost of treatment, and need to obtain time off work to get treatment. Three out of five patients surveyed online ranked the importance of less frequent injections as important or extremely important. Four patients who were interviewed over the telephone expressed the advantages of Iluvien in terms of the reduced number of injections and associated discomfort, less worry about injection-related infections, less time off work to attend appointments, increased independence, and a sense of “permanency” in their vision. Although the submitted pharmacoeconomic evidence and CADTH reanalyses capture adverse events from injection-related infections such as endophthalmitis and retinal detachments, the benefits associated with the convenience of less frequent injections were not explicitly modelled.

Conclusions

CADTH identified several key limitations with the manufacturer's model. Based on a series of reanalyses, CADTH estimated that the ICUR of FA implant plus BSC compared with BSC alone was $91,452 per QALY. At a willingness to pay of $50,000 per QALY, FA implant plus BSC was associated with a 4% probability of being cost-effective compared with BSC alone. A price reduction of more than 45% is required for FA implant plus BSC to achieve an ICUR of less than $50,000 per QALY compared with BSC alone.

However, given the limitations with the model structure, data sources, and uncertainty associated with the extrapolation of long-term costs and consequences that could not be adequately addressed in the CADTH reanalyses, caution should be applied in interpreting the cost-effectiveness results. Several subgroup analyses and scenario analyses were conducted to capture some of the uncertainties, and the ICURs in these analyses ranged between $72,069 and $177,495 per QALY gained.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 5: CADTH Cost Comparison Table of Treatments for Adults with Diabetic Macular Edema

Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost per Eye ($)
Fluocinolone acetonide (Iluvien)	**0.19 mg**	**Intravitreal implant**	**7,770.0000[a]**	**One 0.19 mg intravitreal implant lasting 36 months**	**7,700 (for 36 months)** **2,590 (per year)**
Glucocorticoid Receptor Agonist for the Treatment of Retinal Conditions					
Dexamethasone implant (Ozurdex)	700 mcg (single use)	Intravitreal implant	1,295.0000[b]	700 mcg intravitreally as needed, with an interval of approximately 6 months	1,295 to 5,180 (1 to 4 implants per year)[c]
Anti-VEGF Therapies for the Treatment of Retinal Conditions					
Aflibercept (Eylea)	2 mg/50 mcL (40 mg/mL) (single-use vial)	Solution for intravitreal injection	1,418.0000	2 mg intravitreally once every 4 weeks for first 5 consecutive doses, then 1 injection every 8 weeks	**First year:** 12,762 (9 injections) **Subsequent years:** 8,508 to 9,926 (6 to 7 injections)
Ranibizumab (Lucentis)	10 mg/mL (2.3 mg/0.23 mL single-use vial or 1.65 mg/0.165 mL pre-filled syringe)	Solution for intravitreal injection	1,575.0000	0.5 mg intravitreally monthly until maximum visual acuity achieved (i.e., stable for 3 consecutive months); resume if recurrence of vision loss	**Maximum:** 18,900 (12 injections) **Observed in trials:** 11,025 in first year (7 injections)[d] **Subsequent years:** 4,725 to 6,300 (3 to 4 injections)[d]
Other Anti-VEGF Therapies Not Indicated for DME					
Bevacizumab (Avastin)	100 mg/4 mL 400 mg/16 mL	Solution for injection	519.1776[e] 2,076.7104[e]	1.25 mg intravitreally every 4 to 6 weeks[f]	4,673 to 6,749 (9 to 13 injections)
Bevacizumab (MVASI)	100 mg/4 mL 400 mg/16 mL	Solution for injection	385.9400[g] 1,543.7700[g]	1.25 mg intravitreally every 4 to 6 weeks[f]	3,473 to 5,017 (9 to 13 injections)

Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost per Eye ($)
Other Corticosteroid Therapies Not Indicated for DME					
Triamcinolone acetonide (Kenalog-40, generic)	40 mg/1 mL 200 mg/5 mL	Injectable suspension	8.9600 31.6500	1 to 4 mg intravitreally every 3 to 4 months[h]	Up to 27 to 36 (3 to 4 injections)
Triamcinolone acetonide (Triesence)	40 mg/1 mL (single-use vial)	Suspension for intravitreal injection	42.5900[i]	1 to 4 mg intravitreally every 3 to 4 months	128 to 170 (3 to 4 injections)
Other Treatments					
Laser photocoagulation	NA	NA	182.7500[j]	As needed when re-treatment criteria met, no more than every 12 weeks[k]	183 to 914 (1 to 5 treatments)

DME = diabetic macular edema; NA = not applicable; VEGF = vascular endothelial growth factor.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2019), unless otherwise indicated, and do not include costs of product dispensing, dose preparation, or administration. Annual period assumes 52 weeks, or 13 × 4 weeks per year (364 days for all comparators). The calculated annual doses are based on product monograph, where available. When multiple formulations were available, the least expensive type was used to calculate costs. All injected comparators are assumed to be single-use vials, with leftover product being wasted.

[a] Manufacturer-submitted price.[1]

[b] Quebec formulary list price (IQVIA Delta PA, June 2019).[27]

[c] Dosing based on MEAD trials. Patients received one to seven doses over three years (mean 4.1 doses). Re-treatment was available every three months.[28]

[d] Based on rounded average dosing in the RESTORE study: seven doses in year 1, of which the first three monthly injections were administered to all patients,[29] and a mean of three to four doses per year over years 2 and 3.[30]

[e] Wholesale acquisition price based on IQVIA DeltaPA database (June 2019) is $129.7944 per mL in 4 mL or 16 mL vial.[27]

[f] Dosing based on American Academy of Ophthalmology.[31]

[g] Based on price reported in CADTH biosimilar summary dossier for bevacizumab (MVASI).[32]

[h] Dosing based on the Standard Care Versus Corticosteroid for Retinal Vein Occlusion (SCORE) study.[33]

[i] Wholesale acquisition price based on IQVIA DeltaPA database (June 2019).[27]

[j] Ontario Schedule of Benefits: Physician Services Under the *Health Insurance Act* (effective March 1, 2016), code E154.[34]

[k] Dosing based on VIVID DME trial.[35]

Appendix 2: Additional Information

Table 6: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	Lack of consistency between the submitted pharmacoeconomic report and model		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking “poor”	Rationale for certain aspects of the economic model not clear		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 7: Authors information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis	X		

CDR = CADTH Common Drug Review.

Appendix 3: Summary of Other HTA Reviews of Drug

The cost-effectiveness of fluocinolone acetonide (FA) intravitreal implant for the treatment of DME has been assessed three times by the National Institute for Health and Care Excellence (NICE) in England,[26,36,37] twice by the Scottish Medicines Consortium (SMC),[25] and once by the National Centre for Pharmacoeconomics (NCPE)[23] in Ireland. NICE and SMC reviews are summarized in Table 8 and Table 9, respectively. The NCPE did not recommend FA implant for the treatment of vision impairment associated with chronic DME considered insufficiently responsive to available therapies.[23]

Table 8: National Institute for Health and Care Excellence Findings

	NICE (2013 Rapid Review)[24a]
Treatment	FA 190 mcg intravitreal implant for treating chronic DME after an inadequate response to prior therapy, releasing 0.2 mcg per day for approximately 36 months
Price	£5,500 (C$8,855) per implant that is further reduced with PAS (1.00 British pound = 1.61 Canadian dollars; 2013)[38]
Similarities with CDR submission	• CUA comparing FA implant with BSC, modelled as a 15-year Markov model with 3-month cycles • 14 health states: 13 visual acuity health states of 5 ETDRS letter intervals and a death state • Transition probabilities were based on FAME studies • 25% QALY uplift was applied for patients who received bilateral treatment
Differences with CDR submission	• Target population: chronic DME; subgroup analysis also submitted for patients treated in a pseudophakic eye • 20% unilateral BSE treatment, 40% unilateral WSE treatment, and 40% bilateral treatment • FA implant re-treatment only for patients who responded (≥ 5-letter BCVA improvement) after 3 years; 5% were assumed to improve by 5 letters and 3% were assumed to worsen by 5 letters every 3 months • Transition probabilities for extrapolated period after 3 years based on last 30 months of FAME studies for pseudophakic subgroup • Utility value for treatment in WSE was assumed to be 30% of utility benefit associated with treatment in BSE • Model parameters and assumptions were intended to reflect an English population • Model also compared FA implant with laser photocoagulation using data from DRCR protocol B • Annual cost of blindness was applied to patients who fall below 35 letters BCVA
Manufacturer's results	ICUR of £22,600 per QALY gained in the original submission
Issues noted by the review group	• Use of health-state distributions from FAME trials for first three years did not allow for exploration of different scenarios; more appropriate to use transition probability matrices • Applied a minimum 5-letter improvement re-treatment criterion between baseline and 36 months; more realistic criterion: minimum 10-letter improvement • A model structure that modelled patients as being able to receive treatment in both eyes would have been more appropriate than making an ad-hoc adjustment to the output of a model in which patients could receive treatment in only one eye • Limitations with utilities to model HRQoL in patients with chronic DME, sourced from study of patients with AMD and based on BSE • Uncertain clinical effectiveness of pseudophakic subgroup due to small number of patients with pseudophakic lens in the FAME trials
Results of reanalyses by the review group	Without PAS, ICURs for the chronic DME population ranged from £47,600 to £80,000 per QALY, depending on the utility values used; ICURs for the pseudophakic subgroup ranged from £29,700 to £50,600 per QALY; With PAS, ICURs ranged from £37,600 to £63,500 per QALY for the chronic DME population, and £17,500 to £30,000 per QALY for the pseudophakic subgroup
Recommendation	Recommended as an option for treating chronic DME that is insufficiently responsive to available therapies only if: • the implant is to be used in an eye with an intraocular (pseudophakic) lens and • the manufacturer provides FA implant with the discount agreed to in the PAS

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; BSC = best supportive care; BSE = better-seeing eye; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide; GBP = British pound sterling; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; PAS = patient access scheme; QALY = quality-adjusted life-year; WSE = worse-seeing eye.

[a] The cited guidance was reviewed in June 2018. NICE recommendation did not change after the latest review.[36]

Table 9: Scottish Medicines Consortium Findings

	SMC (2014 Resubmission)[25]
Treatment	FA 190 mcg intravitreal implant for treatment of vision impairment associated with chronic DME, considered insufficiently responsive to available therapies
Price	£5,500 (C$10,010) per implant; the HTA also considered a PAS submitted by the manufacturer (1.00 British pound = 1.82 Canadian dollars; 2014)[38]
Similarities with CDR submission	• CUA comparing FA implant with BSC, modelled as a 15-year Markov model with 3-month cycles • 14 health states: 13 visual acuity health states of 5 ETDRS letter intervals and a death state • Transition probabilities were based on the FAME studies
Differences with CDR submission	• Target population is patients with visual impairment due to chronic pseudophakic DME with an inadequate response to prior therapy; consequently, cataract surgery was not modelled • 40% unilateral BSE treatment, 20% unilateral WSE treatment, and 40% bilateral treatment • FA implant re-treatment only for patients who responded (≥ 10-letter BCVA improvement) and had below 20/32 vision (BCVA of 75 letters) after 3 years • Transition probabilities beyond the first 3 years were based on last 30 months of the FAME studies • Utility value in WSE was assumed to be 30% of utility benefit associated with treatment in BSE • For bilateral treatment, utility benefit for WSE was assumed in addition to the BSE utility • Model parameters and assumptions were intended to reflect a Scottish population
Manufacturer's results	With the PAS, the incremental cost-utility ratio (ICUR) was £9,464 per quality-adjusted life-year (QALY); using the Brown et al. (1999) source[39] increased the ICUR up to £16.7,000 per QALY; allowing FA implant re-treatment within the first 3 years and assuming higher proportion of WSE-treated patients led to ICURs between £14.6,000 and £25.5,000 per QALY, depending on the utility values used
Issues noted by the review group	• Observed re-treatments during the first 3 years of the FAME trials were not modelled in the economic analysis; this is not realistic, as the summary of product characteristics for FA implant states possible re-treatment after 12 months • Limitations of clinical data for pseudophakic patients, including small patient numbers
Results of reanalyses by the review group	A range of scenario analyses, including: re-treatment of all responders at 3 years, increased proportion of patients treated in WSE, increased WSE utility gain, and assumption of no WSE benefit in bilateral treatment resulted in ICURs below £12,000 per QALY with PAS. ICURs ranged from £13,000 to £23,000 per QALY with PAS if Brown et al. (1999)[39] utility values were used
Recommendation	Accepted for restricted use: • only in patients in whom the affected eye is pseudophakic (has an artificial lens after cataract surgery) and • re-treatment would take place only if the patient had previously responded to treatment with FA implant and subsequently BCVA had deteriorated to less than 20/32

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; BSC = best supportive care; BSE = better-seeing eye; CUA = cost-utility analysis; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide; HTA = health technology assessment; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PAS = patient access scheme; SMC = Scottish Medicines Consortium; WSE = worse-seeing eye.

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis (CUA) comparing treatment of fluocinolone acetonide (FA) intravitreal implant plus best supportive care (BSC) with BSC alone in patients (mean age 63.4 years) with diabetic macular edema (DME) who had received at least one prior laser treatment, as per the FAME registration trials.[4] BSC included the use of concomitant therapies such as triamcinolone acetate, dexamethasone, bevacizumab, ranibizumab, and laser therapy (Table 10).

Table 10: Average Annual Number of Concomitant Therapies by Year and Treatment.

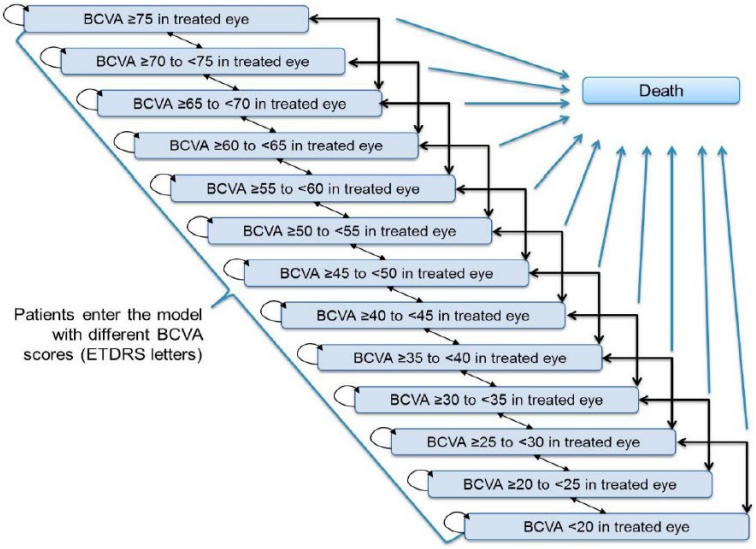
Concomitant Therapy	FA Implant + BSC			BSC Only		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Laser	0.39	0.30	0.26	0.71	0.24	0.34
Triamcinolone acetate	0.05	0.03	0.06	0.24	0.17	0.17
Dexamethasone	0.00	0.00	0.00	0.01	0.00	0.00
Bevacizumab	0.01	0.01	0.01	0.05	0.05	0.07
Ranibizumab	0.00	0.00	0.00	0.00	0.02	0.09

BSC = best supportive care; FA = fluocinolone acetonide.

Source: Manufacturer's pharmacoeconomic submission.[4]

The CUA was structured as a Markov cohort consisting of 14 health states, including 13 visual acuity health states based on the best-corrected visual acuity (number of Early Treatment Diabetic Retinopathy Study [ETDRS] letters) of a treated eye (only the better-seeing eye [BSE] was tracked for bilaterally treated patients), and an absorbing death state (Figure 1).

Figure 1: Manufacturer's Model Structure



BCVA = best-corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study.

Source: Adapted from manufacturer's pharmacoeconomic submission.[4]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Baseline distribution of patients across visual acuity health states for each treatment arm was based on the full analysis population of the pooled FAME trials. Baseline mean age and gender distribution parameters were based on the chronic diabetic macular edema (DME) population subgroup (at least three years since diagnosis of DME) from the pooled FAME trials.	Appropriate. Acceptable. Although referenced mean age and gender distribution from the full FAME trial population would have been preferred, the values do not appear to be drastically different from the demographic profile of the overall FAME trial and are not expected to significantly impact model results.
Natural history	For patients who received fluocinolone acetonide (FA) implant, the treatment discontinuation rate was based on a subgroup of patients from the FAME trials who had been diagnosed with DME for at least three years.	Acceptable. Although discontinuation rates from the full FAME trial population would have been preferred, the values do not appear to be drastically different and do not appear to significantly impact model results.
Efficacy	The distribution of patients across visual acuity health states for each treatment arm for the first three years was based on the full analysis population of the pooled FAME trials. Transition probabilities for visual acuity changes beyond the first three years were based on the last year of the pooled FAME trials to avoid the development of treatment-related cataracts potentially biasing the results.[4] Most cataract surgeries in the FAME trials had occurred in the first two years (FAME-A: 81.8% of cataracts in the sham injection arm, 98.0% of cataracts in the low-dose FA implant arm; FAME-B: 85.7% of cataracts in the sham injection arm, 92.2% of cataracts in the low-dose FA implant arm).[5,6]	Acceptable. However, the use of transition probabilities and relative risks would have been more appropriate, as these explicitly capture the movement of patients between health states over time and would allow for efficacy during the first three years to be explored probabilistically. Uncertain. Cataracts remains a possible outcome for the HC-indication population with corticosteroid treatment. Truncating data available for extrapolation from three years to one year introduces more uncertainty in the extrapolation approach, and the trade-off between any potential bias associated with cataracts and data available for extrapolation is unclear. The results of CADTH reanalysis 2 indicates that the use of the truncated data does not have a large impact on ICUR. It is also uncertain whether treatment-effect plateauing could occur, or whether FA implant could be administered indefinitely every three years as modelled. FAME trial data may not be able to address these uncertainties.
Utilities	Visual acuity health-state utilities were based on time–trade-off (TTO) utility values elicited from US patients with age-related macular degeneration (AMD).[9]	Inappropriate. The proportion of patients with diabetic retinopathy or DME is not reported in the Brown et al., 2000 study and the generalizability to the DME population is uncertain. Furthermore, the utility values from the study reflect the relationship between the BSE and health-state utility. It is unknown whether this relationship would also be similar for the WSE. The literature suggests the WSE has little impact on health utility in patients with AMD.[11,16] Furthermore, it is uncertain whether the TTO utility values based on the study are generalizable to the DME population. Utility values based on HUI3, a utility measure validated in the Canadian population, is available in the literature and has a statistically significant relationship to changes in visual acuity in the BSE and WSE.[16]

Data Input	Description of Data Source	Comment
Adverse events	Treatment-specific incidences of elevated intraocular pressure, cataract surgery, glaucoma procedure, and vitrectomy were based on the pooled FAME trials.	Appropriate.
	Incidence of cataract and glaucoma in DME patients beyond three years or in patients who do not receive FA implant were based on US observational studies.[7,8]	It is uncertain how reflective these observational studies are of the current DME population, given advances in diabetes management since the time of the studies.
	Injection-dependent rates of endophthalmitis and retinal detachment were also based on the pooled FAME trials.	Appropriate.
Mortality	Mortality in the general population was sourced from the UK Office for National Statistics.[4]	Inappropriate to use UK general mortality data when Canada-specific mortality data are available from Statistics Canada.[19]
	The relative risk (RR) of mortality for DME patients versus general population was derived as a product of two hazard ratios (HRs): HR of mortality in patients with diabetes versus general population from Mulnier et al.,[14] and the HR of patients with DME versus patients with diabetes from Hirai et al.[15]	Inappropriate. HRs from the cited studies were treated as RRs and applied to probability of mortality instead of hazard rates. The HR from Mulnier et al., also reflects a comparison of patients with diabetes compared with populations that do not have diabetes.[14] It is inappropriate to apply this HR to the general population, as a proportion of the general population already has diabetes. Furthermore, it is uncertain whether the cited studies reflect the Canadian population. It should be noted that the prevalence of diabetes in Mulnier et al. was approximately 1.5%, whereas the Canadian prevalence reported by the Public Health Agency of Canada in 2017 was 8.1%.[40]
Resource Use and Costs		
Drug	Drug price for FA implant was based on the manufacturer's submitted price.[4]	Appropriate.
	Other drug prices were based on IMS claims data from 2015–2017, reflecting Ontario and Quebec formulary prices.[4]	Uncertain whether these would reflect more recent prices.
Administration and monitoring	Unit costs for drug administration and other professional services were based on the Ontario Schedule of Benefits.[4]	Appropriate.
	Resource use for optical coherence tomography, fluorescein angiography, and office visits were based on the FAME trials and validated with Canadian clinical experts.[4]	Data sources are appropriate. However, it is unclear whether the input values in the model reflect the range of values observed in the manufacturer's validation survey of Canadian clinical experts. This uncertainty is not captured in the model, as the resource use inputs are modelled deterministically.
Adverse events	Resource use for adverse events was based on consultations with Canadian clinical experts.[4]	Appropriate.
Blindness	Cost of blindness associated with non–eye-related medical costs (e.g., falls, depression, and long-term care stay) was based on a 2014 US annual cost of care estimate,[13] and inflated to 2018 Canadian dollars.	Inappropriate. Uncertain whether these costs would reflect costs in Canada. The costs reported in Pershing et al., 2014 were based on a US study based on 1999 to 2003 Medicare claims data.[12,13] Cost estimates that are more reflective of Canadian costs are available in literature.[18]

AMD = age-related macular degeneration; BSE = better-seeing eye; DME = diabetic macular edema; FA = fluocinolone acetate; HC = Health Canada; HR = hazard ratio; HUI3 = Health Utility Index Mark 3; ICUR = incremental cost-utility ratio; RR = relative risk; TTO = time trade-off; WSE = worse-seeing eye.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
FA implant plus BSC versus BSC alone is an appropriate comparison.	Inappropriate. According to the clinical expert consulted by CADTH, it is unclear whether the composition of treatments within the BSC arm of the FAME trial reflects clinical practice in Canada. Anti-VEGF treatments would typically be used more often in Canada. The FAME trials also excluded aflibercept, an anti-VEGF therapy currently reimbursed in Canada. It would have been more appropriate to compare FA implant with individual comparators.
Time horizon is 15 years.	Uncertain. A 15-year time horizon may not comprehensively capture the chronic nature of DME; approximately half of the patients are still alive at the end of the model. However, given the lack of evidence regarding re-treatment, it is unclear whether the HC-indicated population would receive FA implant over 15 years.
Extrapolation based on efficacy, safety, and discontinuation rates from FAME trials and other data sources in the model reflect long-term trends.	It is uncertain whether the efficacy, safety, and discontinuation trends observed in the short-term data would be preserved over the 15-year time horizon. There is significant uncertainty associated with the results based on the 15-year time horizon, as the model requires extensive extrapolation based on the FAME trials and other sources that do not reflect Canadian practice. The majority of incremental QALYs attributed to FA implant (61%) is from the extrapolated period of the model.
30% of bilateral treatment patients received FA implant in one eye and BSC in the other eye; remaining 70% of bilateral-treatment patients received FA implant in both eyes.	Uncertain. Although the clinical expert consulted by CADTH confirmed that some bilateral-treatment patients receive different treatment for each eye, the exact proportion is uncertain.
FA implant is assumed to be administered only once in the first three years of the model.	Inappropriate. The efficacy data are based on the approximately 24% of patients receiving multiple doses of FA implant;[4] however, this is not accounted for in the model costs, which underestimates the ICUR.
Excluding FA implant, other DME treatments are not administered after three years from the start of the model.	Inappropriate. Key comparator treatment costs should be comprehensively considered in the economic evaluation.
Treatment response definition is based on ≥ 15 ETDRS letters improvement.	Acceptable. A loss or gain of 10 to 15 letters is the most commonly used MCID in clinical studies.
FA implant treatment response is determined 36 months after treatment.	Inappropriate. According to the clinical expert consulted by CADTH, treatment response is assessed after one month, and another treatment is considered for non-responders after this point.
There is an additional 25% utility gain associated with bilateral treatment compared with unilateral treatment.	The incremental utility gain associated with treating the WSE in addition to the BSE is uncertain. Although the manufacturer relied on the recommendation of Canadian clinical experts that bilateral treatment would provide additional HRQoL benefit, the clinical expert consulted by CADTH considered it reasonable to assume that no additional HRQoL benefit would be gained from bilateral treatment compared with BSE treatment. The manufacturer also referred to a study that found a statistically significant relationship between WSE visual acuity and the NEI VFQ-25 HRQoL measure; the same study found that WSE visual acuity did not have a statistically significant relationship with HUI3 utility values.[11] Furthermore, the Brown et al., 2000 utility values used in the model are based on analyses that did not consider WSE visual acuity.[9] Adding incremental utility based on WSE visual acuity risks double counting the health utility gains associated with change in visual acuity.

Assumption	Comment
Utility decrements associated with adverse events were not directly modelled because the modelled adverse events primarily affect visual function and changes in utility because changes in visual function were already captured in the model.	Acceptable. According to the clinical expert consulted by CADTH, key adverse events for DME treatments are not expected to affect quality of life outside of visual function. However, not all potentially relevant adverse events may have been captured. Arterial thromboembolic event is an adverse event potentially related to anti-VEGF use[41] and would have warranted consideration, as anti-VEGF drugs were included in BSC treatments. Costs associated with vision-related falls and depression were included, but the potential impact of vision-related falls and depression on health utility was not considered.
Beyond three years from the start of the model, adverse events, except for cataract surgery and glaucoma, do not occur for patients who are treated with BSC.	Inappropriate. Treatment-related adverse events should be modelled over the entirety of the model time horizon. Endophthalmitis and retinal detachment were considered in the model beyond three years for patients who receive FA implant plus BSC. It is inconsistent to not consider these adverse events for patients treated with BSC alone.
Beyond three years from the start of the model, only cataract surgery, glaucoma, endophthalmitis, and retinal detachment occur for patients who are treated with FA implant plus BSC.	Inappropriate. Treatment-related adverse events should be modelled over the entirety of the time horizon.
Cost of blindness, associated with non–eye-related medical costs, applies to a patient when their BSE visual acuity (whether unilaterally or bilaterally treated) falls below 65 ETDRS letters.	Inappropriate. Cost of blindness should be applied to patients with visual acuity of fewer than 35 ETDRS letters (equivalent to visual acuity of legal blindness, 20/200[10]).

BSC = best supportive care; BSE = better-seeing eye; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HC = Health Canada; HR = hazard ratio; HRQoL = health-related quality of life; HUI3 = Health Utility Index Mark 3; MCID = minimal clinically important difference; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; QALY = quality-adjusted life-year; VEGF = vascular endothelial growth factor; WSE = worse-seeing eye.

CADTH Common Drug Review Reanalyses

Table 13 describes the health-utility input parameters used in the manufacturer's base case and the revised parameters in CADTH reanalysis 6 and the CADTH base case.

Table 13: Updated Health-State Utilities for Unilaterally Treated Better-Seeing and Worse-Seeing Eye

Visual Acuity Health State	Manufacturer's Base Case[a] Mean Health Utility		CADTH Reanalysis[b] Mean Health Utility (95% CI)	
	BSE	WSE	BSE	WSE
BCVA ≥ 75 in treated eye	0.89	0.81	0.81 (0.71 to 0.91)	0.90 (0.81 to 1.00)
BCVA ≥ 70 to < 75 in treated eye	0.81	0.76	0.81 (0.71 to 0.91)	0.90 (0.81 to 1.00)
BCVA ≥ 65 to < 70 in treated eye	0.81	0.72	0.81 (0.71 to 0.91)	0.90 (0.81 to 1.00)
BCVA ≥ 60 to < 65 in treated eye	0.81	0.68	0.81 (0.71 to 0.91)	0.90 (0.81 to 1.00)
BCVA ≥ 55 to < 60 in treated eye	0.57	0.64	0.53 (0.37 to 0.70)	0.81 (0.66 to 0.95)
BCVA ≥ 50 to < 55 in treated eye	0.57	0.60	0.53 (0.37 to 0.70)	0.81 (0.66 to 0.95)
BCVA ≥ 45 to < 50 in treated eye	0.545	0.56	0.53 (0.37 to 0.70)	0.81 (0.66 to 0.95)

Visual Acuity Health State	Manufacturer's Base Case[a] Mean Health Utility		CADTH Reanalysis[b] Mean Health Utility (95% CI)	
	BSE	WSE	BSE	WSE
BCVA ≥ 40 to < 45 in treated eye	0.545	0.52	0.53 (0.37 to 0.70)	0.81 (0.66 to 0.95)
BCVA ≥ 35 to < 40 in treated eye	0.545	0.48	0.40 (0.28 to 0.52)	0.51 (0.40 to 0.62)
BCVA ≥ 30 to < 35 in treated eye	0.52	0.44	0.40 (0.28 to0.52)	0.51 (0.40 to 0.62
BCVA ≥ 25 to < 30 in treated eye	0.52	0.40	0.40 (0.28 to0.52)	0.51 (0.40 to 0.62
BCVA ≥ 20 to < 25 in treated eye	0.52	0.36	0.40 (0.28 to0.52)	0.51 (0.40 to 0.62
BCVA < 20 in treated eye	0.40	0.32	0.40 (0.28 to0.52)	0.51 (0.40 to 0.62

BCVA = best-corrected visual acuity; BSE = better-seeing eye; CI = confidence interval; WSE = worse-seeing eye.

[a] Source: Time–trade-off values from Brown et al., 2000[9] and Brown et al., 1999.[39] The difference between the best and the worst WSE visual acuity health states were assumed to be the same as that for BSE health states. WSE health utilities were assumed to vary equally between health states.[4]

[b] Source: Health Utility Index Mark 3 values for BSE and WSE from Heintz et al., 2012.[16]

CADTH could not address the remaining limitations associated with model structure, data sources, and uncertainty associated with the extrapolation of long-term costs and consequences. Consequently, several subgroup analyses and scenario analyses were explored:

S1a. Unilaterally treated in the BSE

S1b. Unilaterally treated in the worse-seeing eye (WSE)

S1c. Bilaterally treated (70% of those treated bilaterally received FA implant plus BSC group in both eyes; 30% of those treated bilaterally received only FA implant plus BSC in one eye and BSC alone in the other eye)

S1d. Bilaterally treated (all patients in the FA implant plus BSC group received FA implant plus BSC in both eyes)

S2 Patients with pseudophakic lens and at least a three-year history of DME

S3a. 10-year time horizon

S3b. Five-year time horizon

S3c. Three-year time horizon (no extrapolation)

In these analyses, the ICUR for FA implant plus BSC compared with BSC alone ranged between $72,069 and $177,495 per QALY gained (Table 14).

Table 14: CADTH Scenario Analyses (Fluocinolone Acetate Implant Plus Best Supportive Care Versus Best Supportive Care Alone)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
Subgroup Analyses					
S1a	Unilaterally treated BSE	FA implant + BSC	36,690	8.75	–
		BSC	22,221	8.55	–
		Incremental	*14,469*	*0.20*	*72,069*
S1b	Unilaterally treated WSE	FA implant + BSC	29,665	8.75	–
		BSC	14,089	8.55	–
		Incremental	*15,576*	*0.20*	*77,583*
S1c	Bilaterally treated (70% FA implant plus BSC bilaterally, 30% FA implant plus BSC in one eye, BSC only in the other eye)	FA implant + BSC	48,861	8.75	–
		BSC	23,229	8.55	–
		Incremental	*25,632*	*0.20*	*127,674*
S1d	Bilaterally treated (100% FA implant plus BSC in both eyes)	FA implant + BSC	53,646	8.75	–
		BSC	23,229	8.55	–
		Incremental	*30,416*	*0.20*	*151,505*
S2	Patients with pseudophakic lens and at least a three-year history of DME	FA implant + BSC	40,200	8.75	–
		BSC	20,713	7.97	–
		Incremental	*19,486*	*0.77*	*25,154*
Scenario Analyses					
S3a	10-year time horizon	FA implant + BSC	30,708	6.10	–
		BSC	13,545	5.95	–
		Incremental	*17,163*	*0.15*	*115,970*
S3b	5-year time horizon	FA implant + BSC	21,700	3.18	–
		BSC	7,987	3.09	–
		Incremental	*13,713*	*0.09*	*152,661*
S3c	3-year time horizon (no extrapolation)	FA implant + BSC	16,849	1.94	–
		BSC	5,565	1.87	–
		Incremental	*11,284*	*0.06*	*177,495*

BSC = best supportive care; BSE = better-seeing eye; DME = diabetic macular edema, FA = fluocinolone acetate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; WSE = worse-seeing eye.

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