Common Drug Review

Pharmacoeconomic Review Report

January 2014

Drug	ocriplasmin (Jetrea) (125 mcg intravitreal injection)
Indication	For the treatment of symptomatic vitreomacular adhesion
Listing request	As per indication for single-use only (subsequent injections in the same eye will not be covered) and diagnosis should be confirmed through optical coherence tomography
Manufacturer	Alcon Canada Inc.

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ABBREVIATIONS

AE	adverse event
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
BSE	better-seeing eye
CI	confidence interval
CUA	cost-utility analysis
ETDRS	Early Treatment Diabetic Retinopathy Study
ICUR	incremental cost-utility ratio
LY	life-year
MH	macular hole
OCT	optical coherence tomography
QALY	quality-adjusted life-year
SA	sensitivity analysis
VMA	vitreomacular adhesion
VMT	vitreomacular traction
WSE	worse-seeing eye

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ocriplasmin (Jetrea)
Objective	"To determine the cost-effectiveness of a single injection of JETREA for the treatment of symptomatic vitreomacular adhesion (sVMA) including when associated with macular hole (MH), compared with "watchful waiting", from both the public-payer and societal perspectives."
Type of economic evaluation	CUA
Target population	Patient aged 18 years or older, presence of focal vitreomacular adhesion, defined as vitreous adhesion to the macula within a 6 mm central retinal field surrounded by elevation of the posterior vitreous cortex, seen on an OCT, and a BCVA of 20/25 or less in the study eye or more in the non-study eye (ETDRS acuity chart).
Treatment	0.125 mg administered by intravitreal injection to the affected eye once as a single dose
Outcome	Non-surgical resolution of VMA on OCT at day 28
Comparator	"Watchful waiting" (medical management)
Perspective	Public payer (societal perspective also considered)
Time horizon	Lifetime (up to 37.5 years)
Manufacturer's results (base case)	$40,124/QALY (Ministry of Health perspective)

Key limitations and CDR estimates	• Ocriplasmin is priced at $3,950 per injection.
	• The manufacturer's analysis included some non-health care costs, which should be excluded in the reference case.
	• Approximately 20% of enrolled patients had bilateral disease, which is likely to be treated sequentially, according to the clinical expert.
	• The trials did not detect significant differences in VA, but did demonstrate differences in the primary outcome of VMT resolution. VA is the primary driver of efficacy in the model, but there is uncertainty regarding the association of VMT and VA over a long time frame (> 6 months) as most of the benefit of ocriplasmin occurs.
	• CDR reference case excludes non-health care costs and includes the cost of ocriplasmin for bilateral disease, which increases the ICUR to $55,544 per QALY. The ICUR was sensitive to examination of uncertainty in longer-term outcomes:
	  ○ The association between VMA resolution and long-term vision is uncertain. If long-term VA transition is assumed to be the same for resolved and unsolved VMA, the ICUR increases to $94,766 per QALY.
	  ○ Spontaneous resolution (> 6 months) of VMA is assumed to be 0%, but two literature sources cited by the manufacturer report greater probabilities (2.2% and 16.5%). Use of these estimates increases the ICUR to $63,264 and $124,621 per QALY respectively.

BCVA = best-corrected visual acuity; CDR = Common Drug Review; CUA = cost-utility analysis; ETDRS = Early Treatment Diabetic Retinopathy Study; ICUR = incremental cost-utility ratio; MH = macular hole; OCT = optical coherence tomography; QALY = quality-adjusted life-year; sMVA = symptomatic vitreomacular adhesion; VA = visual acuity; VMA = vitreomacular adhesion; VMT = vitreomacular traction.

SUMMARY

Background

Ocriplasmin (Jetrea) is being reviewed for the treatment of symptomatic vitreomacular adhesion (sVMA) including when it is associated with macular hole (MH). The recommended dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose. The cost of ocriplasmin is $3,950 per dose.

Summary of Economic Analysis

The manufacturer conducted a cost-utility analysis (CUA) comparing ocriplasmin to "watchful waiting" (medical management), with the option of surgical vitrectomy in either strategy, using data from two phase III randomized controlled trials in VMA patients (TG-MV-006 and TG-MV-007) – *Manufacturer's Pharmacoeconomic Submission*.[1] The reference case time horizon was the patient's lifetime (up to 37.5 years), using the Canadian public-payer perspective. The economic submission is based on a 6-month (trial duration) decision tree and a long-term Markov model.

In the monthly cycle decision tree, a patient with only vitreomacular traction ([VMT]), interchangeable with vitreomacular adhesion [VMA]) can experience non-surgical VMT resolution at day 28, a vitrectomy for VMT depending on the patient's visual acuity (VA), non-surgical resolution or MH at 6 months before they enter into the Markov model. Patients with MH can experience non-surgical MH closure at day 28, a vitrectomy, or non-surgical closure at 6 months. At the end of the decision tree, all patients (VMT + MH) are allocated to the following health states and transit into the long-term extrapolation Markov model: resolved; VMT unresolved without MH; VMT unresolved with MH; VMT resolved with MH (no vitrectomy); VMT resolved with MH (one vitrectomy); VMT resolved with MH (two vitrectomies); or death. Within each Markov cycle, patients can transit between disease health states and between VA health states (stay the same, improve, or get worse). Patients continue to experience the following events: VMT resolution only; MH closure only; VMT resolution and MH closure; or VMT progressing to MH. Each of the health states is associated with a different distribution of VA categories. For patients achieving resolution of VMT, VA was assumed to follow the age-matched general Finnish population's long-term VA decline.[2] VA for patients with persistent VMT (all disease states except "resolved") was assumed to decline gradually, but at a faster rate than the rate in the general population.[3] Adverse events (AEs), including cataract after vitrectomy, retinal tear, retinal detachment, elevated intraocular pressure, and vitreous hemorrhage, were also considered in the model based on rates observed from the clinical trials and data on file.

The majority of the transition probabilities in the decision tree (first 6 months) were taken from the clinical trials, with the exception of the probability of a second vitrectomy for MH and its success rate, which were based on clinical opinion. Transition probabilities in the Markov model were estimated using a regression model based on the trial data, expert opinion, and the literature. Beyond 6 months, the probability of spontaneous resolution of VMA was assumed to be 0%. Quality of life for each VA category was informed by an United Kingdom quality of life study on the general public.[4] In addition, a change in VA in the worse-seeing eye (WSE) was valued at 30% of the same change in the better-seeing eye (BSE). Disutilities for treatment or intervention-associated AEs, metamorphopsia, vitrectomy surgery and cataract were estimated from the published literature[5-8] and assumptions. Higher mortality rates were assigned to patients whose BSE was VA6.[9] Costs were provided by the manufacturer and based on Canadian sources.[10,11]

Results of Manufacturer's Analysis

The manufacturer reported an incremental cost per quality-adjusted life-year (QALY) for ocriplasmin compared with "watchful waiting" of $40,124, using the health-payer perspective.

Interpretations and Key Limitations

Generalizability and inclusion of non–health-care payer costs

Resource utilization associated with visual impairment was obtained from a costing study in wet age-related macular degeneration (AMD) patients; however, generalizability to this population was not discussed. Furthermore, the blindness health state included lost productivity and indirect costs, which should not be included in the base-case analysis as per CADTH guidelines.[12] By excluding the indirect costs of blindness (VA6), the incremental cost-utility ratio (ICUR) increases to $43,657 per QALY.

Bilateral disease

The submission did not consider the cost of treating bilateral disease; in trial data, bilateral disease occurred in 19.9% of patients. According to the clinical expert, both eyes are likely to be treated in practice. The cost of ocriplasmin, as well as the cost of administration, is increased by 20% in the CDR analysis in order to account for the treatment costs in bilateral disease.

Short duration of clinical trial and assumption of long-term relative efficacy

Given the duration of existing trials (6 months) and use of the outcome of VMA resolution (and not VA), it has not been established that long-term differences in the clinically important outcome of VA (the major factor driving quality of life and disease costs) will occur. If the treatment effect is not durable or if it attenuates, the cost-effectiveness ratio will be greater. In the manufacturer's sensitivity analysis, shortening the time horizon to two years resulted in the incremental QALYs decreasing from 0.069 to 0.024 and the cost per QALY increasing to $147,816, highlighting that a majority of the incremental benefit accrued in the model is well beyond the time frame of current randomized control trials (RCTs).

Uncertainty on VMA status and long-term effects on VA

A major assumption is that the greater VMA resolution achieved with ocriplasmin will ultimately result in improved VA (VA is the major determinant of efficacy in the model). As per the CDR Clinical Report, no statistically significant benefit in best-corrected visual acuity (BCVA) was observed with ocriplasmin. However, based on feedback from the clinical expert, a 6-month BCVA for VMA may not be the ideal outcome as a patient's VA typically plateaus and does not demonstrate a stepwise progression until he or she experiences MH. The model is limited by poor quality data (due to the use of different patient populations for each health state as well as a small cohort for VMA) to estimate the long-term VA outcomes in patients with unresolved and resolved VMA.

Uncertainty on long-term, spontaneous resolution probability

The probability of spontaneous resolution of VMA from 6 months to 2 years was set at 0%, but observational data cited by the manufacturer quoted probabilities of 2.2% and 16.5%. Using these values attenuates the relative efficacy of ocriplasmin and leads to a greater ICUR for ocriplasmin.

Results of CDR Analysis

In the CDR new base case where non-health care costs were excluded and costs of ocriplasmin for bilateral disease were included, the ICUR is $55,544 per QALY. In one-way sensitivity analyses exploring long-term efficacy:

- with assumption of no mortality benefit with ocriplasmin: ICUR $65,957 per QALY
- with assumption of the same VA trajectory beyond 6 months for those with and without VMA resolution: ICUR $94,766 per QALY
- literature-cited probabilities of long-term spontaneous VMA resolution of 2.2% and 16.4%: $63,264 and $124,621 per QALY respectively.

Conclusions

For the treatment of VMT, the manufacturer suggests that ocriplasmin is likely to have a cost per QALY of around $40,000 under assumptions of sustained clinical benefit during a 37.5-year time after one injection. In the CDR reference case, where non-health care costs are excluded and treatment costs of bilateral disease are included, the ICUR increases to $55,544 per QALY. When the uncertainty in long-term relative efficacy is explored in sensitivity analysis using the CDR reference case, the incremental cost per QALY increases from $63,000 to > $100,000.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question/Objective

"To determine the cost-effectiveness of a single injection of JETREA for the treatment of symptomatic vitreomacular adhesion (sVMA) including when associated with macular hole (MH), compared with "watchful waiting", from both the public payer and societal perspectives."
(Manufacturer's Submission — Pharmacoeconomic Evaluation, page 15)

1.2 Treatment

A single injection of ocriplasmin.

1.3 Comparators

"Watchful waiting" (with the option of vitrectomy for either treatment strategy) was deemed appropriate by the CDR clinical expert.

1.4 Type of Economic Evaluation

A CUA was undertaken and is appropriate according to the CADTH guidelines.

The primary perspective utilized in the model is that of the Canadian public payer. A secondary analysis was conducted from the societal perspective, taking into account lost workplace productivity, caregiver costs, deadweight losses, and other indirect costs such as home modifications. Details on the lost productivity were provided. Caregiver costs, deadweight losses, and other indirect costs were not defined in the original submission but were provided later in the manufacturer's response.

1.5 Population

Patient population matches the trials' inclusion/exclusion criteria: aged 18 years or older, presence of focal vitreomacular adhesion, defined as vitreous adhesion to the macula within a 6 mm central retinal field surrounded by elevation of the posterior vitreous cortex seen on optical coherence tomography (OCT), and a BCVA of 20/25 or less in the study eye or more in the non-study eye (Early Treatment Diabetic Retinopathy Study [ETDRS] acuity chart). The average age of patients in the model was 71.7 years, and 65.8% of them were female. In both studies, 20% of patients with VMT had bilateral disease, and 73% to 80% were treated in the WSE. The primary trial end point was the non-surgical resolution of VMA on OCT at day 28.

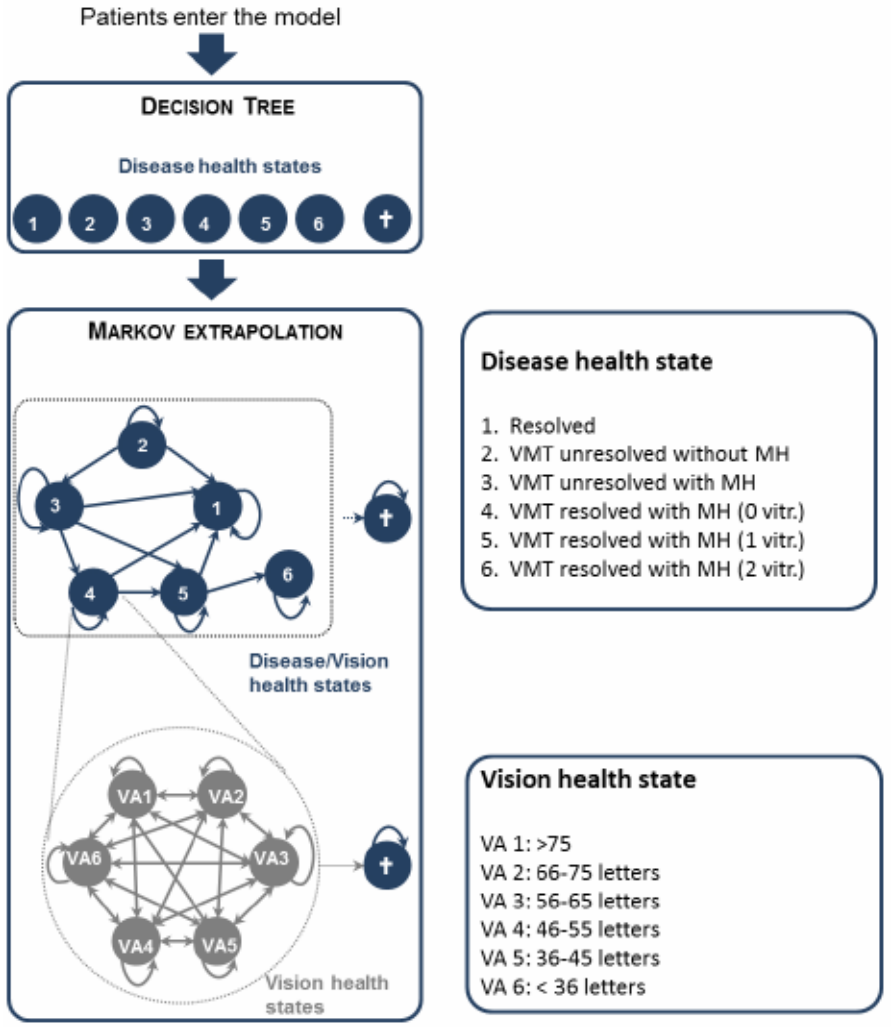
2. METHODS

Table 5 contains a summary of the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure

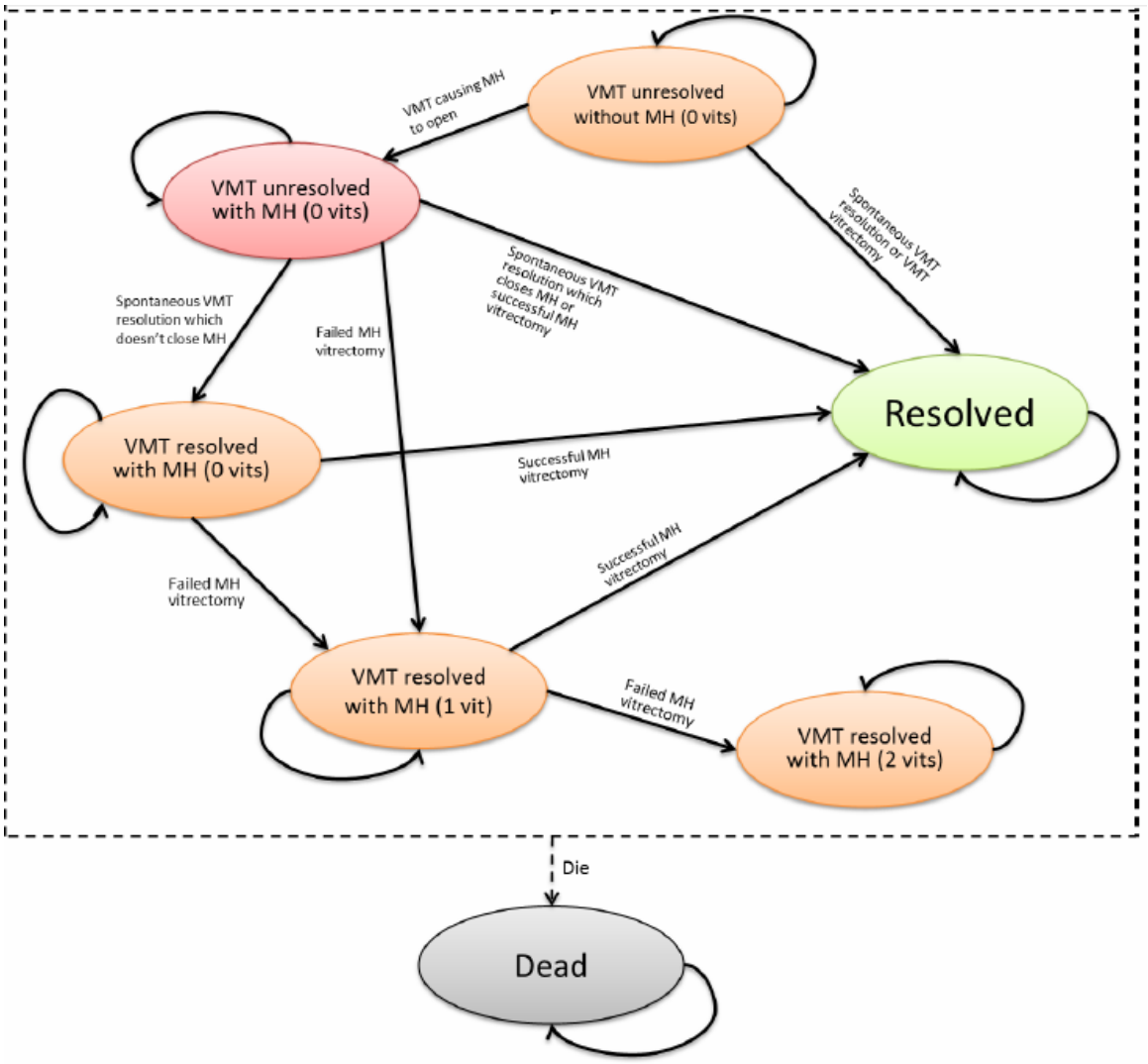
The CUA utilizes two models: a short-term model (0 to month 6) comprising a decision tree that utilizes pooled data from the two RCTs (MIVI-006 and 007), and a long-term Markov extrapolation model (month 6 to lifetime) that simulates disease transition. The disease health states included: resolved VMT; VMT unresolved without MH; VMT unresolved with MH; VMT resolved with MH (no vitrectomy); VMT resolved with MH (one vitrectomy); VMT resolved with MH (two vitrectomies); and, death. Each disease health state is also associated with a different distribution of 6 different vision health states: VA1 (> 75 letters); VA2 (66 to 75 letters); VA3 (56 to 65 letters); VA4 (46 to 55 letters); VA5 (36 to 45 letters); and VA6 (< 36 letters). For example, patients in the resolved and unresolved without MH states would have better VA distribution than patients in other health states. All patients entering the model have VMA, with 23.5% of patients also having MH at baseline. The cycle length in the Markov model was 3 months for the first five years, with annual cycles thereafter. Within each Markov cycle, patients may transition between the six different disease health states based on the following events: VMT vitrectomy, spontaneous VMT resolution, MH vitrectomy (success/fail), spontaneous MH closure, and VMT causing MH. Patients may also stay in the same VA health state, move to another VA health state, or transition to death. The probability of changing VA status over time is different for each of the event health states.

FIGURE 1: MODEL FIGURE



MH = macular hole; VA = visual acuity; VMT = vitreomacular traction.
Source: *Manufacturer's Submission — Pharmacoeconomic Evaluation*, page 17.[1]

FIGURE 2: DISEASE HEALTH STATE TRANSITIONS



MH = macular hole; vit = vitrectomy; VMT = vitreomacular traction.
Source: *Manufacturer's Submission – Pharmacoeconomic Evaluation*, page 29.[1]

2.2 Clinical Inputs

2.2.1 Efficacy

The submission relied upon pooled data from the two phase III clinical studies to estimate the clinical efficacy of ocriplasmin in the first 6 months. Probabilities of VMT vitrectomy, VMT resolution (day 28 and month 6), MH closure (day 28 and month 6), and VA distribution were all derived from trial data. Two parameters (the probability of MH patient undergoing a second vitrectomy and the probability of success of MH closure from the second vitrectomy) could not be estimated from the trial data, so an assumption was made based on expert opinion. For the extrapolation phase (6 months plus), the transition probabilities were estimated using regression models (logit or ordered logit) based on the trial data. The natural history of BCVA was also integrated into the model using a population study from Finland[2] for patients with resolved VMT. VA for patients with persistent VMT was assumed to decline at a faster rate than the rate in the general population using data from a small observational trial (53 patients were followed for 60 months).[3] Beyond 6 months it was assumed that the VMA spontaneous resolution rate was 0%.

2.2.2 Harms

AEs included in the model were cataract after vitrectomy, retinal tear, retinal detachment, elevated intraocular pressure, and vitreous hemorrhage. The probability of these events was estimated from the pooled phase III trial data and was deemed to be appropriate by the clinical expert.

2.2.3 Mortality

All-cause mortality was obtained directly from Statistics Canada; an increased risk of mortality (relative risk = 1.54) with worsening of VA at BCVA level < 56 letters (VA6) was assumed based on observational data from a United States cohort (Christ et al.[9]). This assumption was tested in the manufacturer's and CDR's analyses.

2.2.4 Quality of Life

Quality of life data was collected using the VFQ-25 questionnaire in the two trials, but mapping the VFQ-25 to EQ-5D was not conducted. Details on the utilities used in the model are listed in the Utilities section (Section 2.4).

2.3 Costs

Resource use was considered from the perspective of the Canadian public payer.

2.3.1 Drug Costs

The cost of ocriplasmin injections ($3,950) was obtained from the manufacturer.

2.3.2 Administration Costs

The cost of ocriplasmin injection ($151.84) was obtained from the Ontario Schedule of Benefits. Monitoring costs such as follow-up ($45.84) and OCT ($35.00) were also included in the model for all unresolved patients (resolved VMT or persistent MH) every three months for up to two years, or when resolution occurs.

2.3.3 Event Treatment Costs

Costs associated with treatment-emergent AEs and long-term complications were obtained from the Ontario Schedule of Benefits and the Canadian Institute for Health Information. Mean annual health utilization costs associated with visual impairment for VA states 4 to 5 were derived from a costing study by Cruess et al.[10] on the burden of illness of wet age-related macular degeneration (AMD) in Canada. Direct non-vision-related costs (e.g., accident-related costs, other medical treatment) were included in the model — greater non–vision-related costs were assumed to occur with poorer VA. Mean annual health utilization costs associated with blindness (VA6) was obtained from a report by the Canadian National Institute for the Blind,[11] which included health system costs, lost productivity, care and rehabilitation, other indirect costs, administrative costs, and transfer costs.

2.4 Utilities

Utility associated with the VA health states was obtained from an United Kingdom utility study using the time trade-off instrument.[4] In this study, members of the general public were fitted with contact lenses in both eyes simulating four different VA categories (defined by BCVA in the BSE). To estimate WSE utilities, 30% of the gain in utility for the equivalent change in VA in the BSE was assumed. The manufacturer performed sensitivity analyses on the percentage of how WSE utilities were valued. Disutilities for treatment or intervention-associated AEs, metamorphopsia, and cataract were estimated from literature. Since no direct disutility estimates were identified for vitrectomy surgery, the disutility impact was assumed to be having the surgery-eye blind for 2.5 weeks.

2.5 Time Horizon

The model used a lifetime time horizon (up to 37.5 years) and assumed administration of ocriplasmin would occur only once in the first 6 months. The manufacturer also performed sensitivity analyses on the 6-month to 30-year time horizon.

2.6 Discounting

Both outcomes and costs accrued beyond the first year of the model were discounted at a rate of 5%, as per the CADTH guidelines.

2.7 Validation

Information on model validation was not provided in the submission.

3. RESULTS

3.1 Manufacturer's Base Case

In the reference case, the manufacturer reported that the total cost for ocriplasmin was $12,526, an incremental cost of $2,768 compared with "watchful waiting". Administration of ocriplasmin resulted in additional drug costs of $4,100, and led to reduced costs of vitrectomy/cataract (–$632) and blindness (–$722) compared with "watchful waiting". Treatment with ocriplasmin resulted in 7.22 total QALYs, an additional 0.069 QALY compared with "watchful waiting". Hence, the incremental cost per QALY gained was $40,124 (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of Ocriplasmin ($)	Total Qalys	Incremental QALYs of Ocriplasmin	Incremental Cost Per QALY ($)
Ocriplasmin	12,526	2,768	7.220	0.069	40,124
"Watchful waiting"	9,758		7.151		

QALY = quality-adjusted life-year.
Source: *Manufacturer's Submission – Pharmacoeconomic Evaluation*, page 54.[1]

The manufacturer did not explicitly report a cost per life-year (LY) ratio in the submission. The LY with ocriplasmin was 10.291, compared with 10.285 with "watchful waiting", resulting an additional 0.006 LY gained. Hence the cost per LY was $461,333 per LY. However, the key purported benefit with ocriplasmin was in quality of life and not survival.

3.2 Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using Monte Carlo simulation and one-way deterministic sensitivity analyses, which varied model parameters by using alternative values.

3.2.1 One-Way Sensitivity Analyses

A series of one-way sensitivity analyses (95% confidence interval [CI] of the parameter, unless specified) were conducted by the manufacturer including: probability of moving down a VA state for resolved or unresolved VMT patients; cost of ocriplasmin; cost of injection; cost of vitrectomy; cost of cataract; annual cost of vision loss; cost of monitoring; cost of AEs; utilities; event rates (e.g., probability of cataract, retinal complications, vitreous hemorrhage); time horizon (6 months to 30 years); probability of VMT resolution (day 28 or month 6); and probability of MH closure (day 28 or month 6).

The reference case result for ocriplasmin compared with "watchful waiting" was $40,124 per QALY. The following parameters increased the incremental cost per QALY gained by more than 25% for ocriplasmin:

- Shortened the time horizon to 6 months, 1 year, 2 years, and 10 years: with cost per QALY $429,282, $277,168, $147,815, and $64,165 respectively. Note that the incremental QALYs that accrued for ocriplasmin versus "watchful waiting" were 0.0091, 0.0137, 0.0240 and 0.0501 respectively (compared with reference case lifetime horizon of 0.0690 incremental QALYs).
- Increased the probability of VMT resolution at 28 days for "watchful waiting" (upper 95% CI), cost per QALY was $56,940.
- Increased the probability of VMT resolution at 6 months for "watchful waiting" (upper 95% CI), cost per QALY was $63,830.

By adapting the societal perspective, the cost per QALY was $32,369, although details on the indirect costs included were not provided in the submission.

3.2.2 Probabilistic Sensitivity Analysis

According to the acceptability curves from the probabilistic sensitivity analyses, there is a 67.9% probability that the ICER would fall below the $50,000-per-QALY threshold.

3.2.3 Scenario Analysis (base case value, new value)

The manufacturer also conducted a series of scenario analyses including: change in time limit for vitrectomy and spontaneous resolution (2 years, 1 to 5 years); long-term VA progression in patients with VMA resolution (using data from Finnish and British patients);[13] same long-term VA progression for resolved and unresolved VMT; utilities (Czoski-Murray, Brown);[4,13] change in value of changes in WSE (30%, 0 to 100%); spontaneous resolution rates (trial data, Odrobina, and Hikichi);[3,14] AEs adjusted for vitrectomy exposure; alternative metamorphopsia utility (Fukuda);[6] change in gender distribution (65.8%, 50%); adjusted cost of cataract ($3,507, $536) and vitrectomy ($3,330, $1,069); removal of cost associated with vision loss and blindness; and hazard ratio for mortality due to blindness (1.54, 0).

The following parameters increased the incremental cost per QALY gained by more than 25% for ocriplasmin:

- Assuming long-term (beyond 6 months) deterioration in VA for resolved and unresolved VMT is equal, cost per QALY was $75,284.
- Assuming spontaneous resolution rate observed from 6 months to 2 years of 16.5% (base case 0%), cost per QALY was $98,362.
- Removal of cost associated with vision loss and blindness, cost per QALY was $50,592.

3.3 CDR Analyses

3.3.1 Removal of Non-Health Care Costs

According to the CADTH guidelines, non-health care costs should not be included in the model when the public-payer's perspective is being taken. Since the cost of vision loss included other indirect costs for blindness,[11] CDR's new base case has excluded these costs.

3.3.2 Bilateral Disease

While the trial examined one eye, the two trials enrolled 19.9% of patients with bilateral disease. According to the clinical expert, in practice it is likely that both eyes would be treated sequentially; thus, ocriplasmin treatment costs would be doubled for these patients. It is unclear how this would alter long-term, VA-associated quality of life, given that this is most closely associated with BSE VA.

A second CDR reference case was created that includes the costs of treating bilateral VMT (+20% drug and administration costs).

3.3.3 Uncertain Long-Term Effectiveness

Certain assumptions have been tested in the CDR reanalysis that explored the inherent uncertainty in long-term outcomes. Given the relatively short duration of the trial, lack of data on VA, uncertainty on long-term VA outcomes based on VMT status, and uncertainty in spontaneous resolution rate (which impacts relative efficacy), these were assessed in the CDR references cases as above:

- Exclude non-vision-related medical costs for VA 4 and VA 5.[10] It has not been definitively established that treatment with ocriplasmin would attenuate these non-vision-related health care costs.
- Shorten the time horizon to 1, 2, and 10 years to explore how benefits were accumulated long-term.

- No increased in mortality for blindness (relative risk = 0) given uncertainty that treatment with ocriplasmin would have a beneficial effect on mortality (factors leading to blindness may also result in an increased risk of mortality independent of VA).
- Assume that long-term (> 6 months) deterioration in VA is the same for patients with resolved VMT or unresolved VMT.
- Rate of spontaneous resolution of VMA. The manufacturer used trial data to determine spontaneous resolution probability in the first 6 months (5% at day 28; an additional 7.3% at 6 months for "watchful waiting"), and assumed 0% spontaneous resolution between 6 months and 2 years for both groups (the time limit of two years was tested in the sensitivity analysis below). However, two literature sources cited by the manufacturer indicate that resolution rate after 6 months may be 2.2% to 16.5%. While uncertain, these estimates may be more reasonable than 0%. These two estimates, and a midpoint estimate of 9.4%, were tested.
- Time limit for spontaneous resolution of VMA. In the base case, spontaneous resolution could only occur within the first two years. The manufacturer assessed a time horizon of five years, which CDR analysis also considered in the scenarios where long-term resolution rates from literature sources (2.2% to 16.5%) were used (if 0% spontaneous resolution is assumed in the base case, using a longer time frame in which resolution can occur does not alter results).

TABLE 3: CDR REANALYSIS ICURS FOR OCRIPLASMIN VERSUS "WATCHFUL WAITING"

ICURs of Ocriplasmin versus "Watchful Waiting"			
	Analysis Submitted by Manufacturer ($)	Reanalysis by CDR, Excluding Non-Health Care Costs ($)	Reanalysis by CDR, Excluding Non-Health Care Costs and Including Costs for Bilateral Disease ($)
Base case	40,124	43,657	55,544
Exclude non-vision-related cost	NA	45,516	57,403
Time horizon			
1 year	277,168	222,211	271,092
2 years	147,815	135,233	166,804
10 years	64,165	65,825	82,197
Long-term effectiveness			
No mortality benefit	47,130	51,695	65,957
Same VA trajectory (> 6 months)	75,284	76,229	94,766
2.2% VMT resolution	46,656	50,002	63,264
9.4% VMT resolution	NA	73,946	92,391
16.5% VMT resolution	98,362	100,442	124,621
VMA resolution up to five years			
2.2% VMT resolution	NA	53,933	68,009
9.4% VMT resolution	NA	86,867	108,031
16.5% VMT resolution	NA	113,756	140,761

CDR = Common Drug Review; ICUR = incremental cost-utility ratio; NA = not applicable; VA = visual acuity; VMA = vitreomacular adhesion; VMT = vitreomacular traction.

TABLE 4: CDR ANALYSIS OF ICURS BASED ON VARIOUS PRICE REDUCTION SCENARIOS ($/QALY)

Scenario	ICUR		
	Based on Manufacturer's Analysis ($/QALY)	Scenario Excluding Non-Health Care Costs ($/QALY)	Scenario Excluding Non-Health Care Costs and Including Costs for Bilateral Disease ($/QALY)
Manufacturer's base case ($3,950)	40,124	43,657	55,544
10% price reduction ($3,555)	34,399	37,932	48,674
20% price reduction ($3,160)	28,674	32,207	41,804
30% price reduction ($2,765)	22,949	26,482	34,934
40% price reduction ($2,370)	17,224	20,757	28,064
50% price reduction ($1,975)	11,499	15,032	21,194
60% price reduction ($1,580)	5,774	9,307	14,324
70% price reduction ($1,185)	49	3,582	7,454
80% price reduction ($790)	dominant	dominant	584
90% price reduction ($395)	dominant	dominant	dominant

CDR = Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

4. DISCUSSION

The manufacturer's reference-case analysis is likely an underestimate of the incremental cost-effectiveness ratio of ocriplasmin, due to the inclusion of non-health care costs and not accounting for the costs of treating bilateral disease, which in trial data occurred in approximately 20% of patients presenting with VMT. Further, the trial evaluated a clinically relevant outcome of VMT resolution; however, the association of VMT and MH status with long-term VA outcomes was extrapolated using either relatively poor observational data or assumptions. Given that it is VA (and not VMT status) that directly influences quality of life and additional health care costs, there is substantial uncertainty.

Bilateral disease

While the costs of treating bilateral disease have been added in the CDR reanalysis, only the costs of the interventions and their administration were included. The potential cost savings of vitrectomy and cataracts, costs due to blindness, or changes in quality of life werenot incorporated into this reanalysis. While this is primarily because of a lack of data on contralateral eye outcomes, it may not substantially influence the results — quality-of-life gains are more closely linked to the BSE outcomes; therefore, it is unclear if treatment of bilateral VMT would result in a "better" BSE for a given patient.

Long-term relative efficacy of ocriplasmin

The conducted trials are short, and it is assumed that differences observed at the end of the trials persist throughout the patient's lifetime, leading to greater accrual of VA and quality-of-life gains for the ocriplasmin-treated patients. Using shorter time horizons exemplifies this: the reference case reports incremental QALYs of 0.0690 for ocriplasmin, but only 0.0091 occur in the first 6 months (and 0.0137 at 1 year). This underscores the importance of assumptions influencing long-term relative efficacy.

Uncertainty in long-term relative efficacy

CDR reanalysis explores uncertainty in long-term outcomes using alternate base case (exclusion of non-health care costs and bilateral disease). It could be argued that greater long-term spontaneous resolution probabilities for VMT is a reasonable base case — two literature sources cited by the manufacturer indicate 2.2% and 16.5% spontaneous resolution,[3,14] and the manufacturer's reference case of 0% is not justified in the submission. Scenario analyses that consider multiple areas of long-term uncertainty will result in greater ICUR (for example, using a CDR scenario of excluding non-health care costs and treating of bilateral disease, assuming no mortality benefit and a long-term spontaneous resolution probability of 9.4% resulting in an ICUR of $105,492).

The key limitations associated with the manufacturer's submission are summarized in Table 5:

TABLE 5: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Long-term relative efficacy of ocriplasmin	Conducted trials were short and assumed that differences observed at the end of the trials persist throughout the patients' lifetime.	May overestimate cost-effectiveness. Explored in manufacturer SA and CDR reanalysis.
Impact of resolution and long-term vision	Vision improvement was not observed from the clinical trial extrapolated from VMT status using observational data	May overestimate cost-effectiveness if true improvement in VA not realized.

CDR = Common Drug Review; SA = sensitivity analysis; VA = visual acuity; VMT = vitreomacular traction.

4.1 Issues for Consideration

There are relatively few patients with VMA. This medication is likely to be used only by a retinal specialist. It may be used beyond its indication, but for very select conditions (e.g., MH).

4.2 Patient Input

Visual acuity and avoidance of vitrectomy were important outcomes to patient groups that were included by the manufacturer in the economic submission, although no evidence on vision improvement from the clinical trials was provided. Caregiver costs were also considered from the societal perspective. However, details on how these costs were derived were not provided in the submission.

5. CONCLUSIONS

For the treatment of VMT, the manufacturer suggests that ocriplasmin is likely to have a cost per QALY of around $40,000 under assumptions of sustained clinical benefit over a 37.5-year time frame after one injection. In the CDR reanalysis (reference case) where non-health care costs were excluded and treatment costs of bilateral disease are included, the ICUR increased to $55,544 per QALY. When the uncertainty in long-term relative efficacy is explored in sensitivity analysis using the CDR reference case, the incremental cost per QALY increases from $63,000 to > $100,000.

APPENDIX 1: COST COMPARISON TABLE

The comparators presented in the table below 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.

TABLE 6: COST COMPARISON TABLE

Drug	Strength	Dosage Form	Price ($)	Recommended Dose	Treatment Drug Cost ($)
Ocriplasmin (Jetrea)[a]	2.5 mg / mL	Inj	$3,950.0000	0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose	$3,950

inj = injection.
[a]Manufacturer-submitted price.
Note: No other treatment comparators were identified.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS OCRIPLASMIN RELATIVE TO "WATCHFUL WAITING"?

Ocriplasmin Versus "Watchful Waiting"	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Manufacturer's base case: $40,124 per QALY $461,333 per life-year (not reported in the submission)					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 8: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?		X	
Comments	Did not provide details on all included indirect costs from the societal perspective		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 9: AUTHOR INFORMATION

Authors	Affiliations		
Dr. Charles Piwko Colin Vicente Roman Zibershtein	**PIVINA Consulting Inc.**		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and the right to publish analysis	X		

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