CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Cyclosporine (VERKAZIA)

(Santen Canada Inc.)

Indication: Treatment of severe vernal keratoconjunctivitis in children from four years of age through adolescence.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

ICUR	incremental cost-utility ratio
IOP	intraocular pressure
OTC	over the counter
QALY	quality-adjusted life-year
QUICK	Quality of Life in Children with Vernal Keratoconjunctivitis
RCT	randomized controlled trial
SOC	standard of care
TTO	time trade off
VEKTIS	VErnal KeratoconjunctiviTIs Study
VKC	vernal keratoconjunctivitis

Table 1: Summary of the Manufacturer's Economic Submission

Drug product	Cyclosporine (Verkazia)
Study question	What is the cost-effectiveness of Verkazia plus SOC versus SOC alone for the treatment of severe VKC in children from four years of age through adolescence in Canada?
Type of economic evaluation	Cost-utility analysis
Target population	Children with severe VKC from four years of age through adolescence
Treatment	Cyclosporine (0.1% w/v) plus SOC
Outcome	QALYs
Comparator	SOC: corticosteroid eye drops and/or lubricant eye drops
Perspective	Canadian public health care payer
Time horizon	End of adolescence (i.e., 18 years of age)
Results for base case	ICUR = $85,003 per QALY gained compared with BSC
Key limitations	CADTH identified several key limitations with the submitted analysis: • The model structure did not capture VKC natural history and the relationship between disease severity and costs appropriately. • Relevant comparators were not considered, including immunomodulators (such as tacrolimus) that are currently used off-label in patients with severe VKC, according to the clinical experts consulted by CADTH. • Comparative efficacy was based on VEKTIS, which was noted to have imbalanced treatment and control groups. Efficacy was modelled according to the QUICK questionnaire even though there is a lack of comprehensive evidence regarding the reliability, responsiveness, and validity of this scale. Rather than applying the monthly efficacy that was reported within the trial, an arbitrary standard error (10% of the mean) was used that artificially increased the precision of the efficacy estimates. • Long-term treatment effects are uncertain. The duration of the randomized phase of the clinical trial was four months, and in the submitted base-case model, the majority (96%) of the QALY gains occurred during the extrapolated period, for which there is limited evidence. • The approach to model health utilities applied an unvalidated mapping algorithm to estimate utility decrements based on the trial-reported scores on the two QUICK domains. The impacts of the QUICK domains were considered separately despite being highly correlated, which likely led to double-counting the impact of treatment on health utilities. • Although the risk of elevated IOP from treatment was captured, this was associated with a disutility value specific to glaucoma. The clinical experts consulted by CADTH noted that elevated IOP is asymptomatic and is often managed with minimal impacts on a patient's quality of life. • The costs of OTC lubricant eye drops were included even though these costs are not covered by majority of the Canadian public health care plans.

CDR Estimate(s)	• The CADTH base-case reanalysis addressed some of the limitations by: incorporating monthly efficacy parameters; removing disutilities associated with the QUICK daily activities domain scores and with elevated IOP; and removing lubricant eye drop costs. • In the CADTH base case, the ICUR was $356,474 per QALY gained for cyclosporine 0.1% plus SOC versus SOC alone. A price reduction of more than 81% is required to be considered cost-effective at a threshold of $50,000 per QALY. • CADTH could not address several key limitations of the submitted model, including uncertainties associated with both the model structure and clinical efficacy estimates. The comparative clinical benefits of cyclosporine 0.1% compared with off-label treatments remain unknown. Therefore, careful consideration is required when interpreting the cost-effectiveness results.

ICUR = incremental cost-utility ratio; IOP = intraocular pressure; OTC = over the counter; QALY = quality-adjusted life-year; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; SOC = standard of care; VEKTIS = VErnal KeratoconjunctiviTIs Study; VKC = vernal keratoconjunctivitis; w/v = weight by volume.

Drug	Cyclosporine 0.1% (Verkazia)
Indication	Treatment of severe vernal keratoconjunctivitis in children from 4 years of age through adolescence.
Reimbursement request	As per indication.
Dosage form(s) and route of administration)/strength(s)	Topical ophthalmic emulsion, 0.1% w/v for intraocular administration.
NOC date	24-12-2018
Manufacturer	Santen Canada Inc.

Executive Summary

Background

Cyclosporine (Verkazia) is a topical ophthalmic emulsion (0.1% weight by volume) indicated for the treatment of severe vernal keratoconjunctivitis (VKC) in children from four years of age through adolescence. Cyclosporine 0.1% is supplied as 30 single-use containers containing 0.3 mL unpreserved emulsion at a price of $110.[1] The recommended dose is four drops daily in each affected eye. The dose can be reduced to one drop twice daily once adequate control of signs and symptoms is achieved.[2] According to the clinical expert consulted by CADTH, the treatment is administered in response to VKC symptoms, which may be seasonal. At the submitted price, cyclosporine 0.1% would cost $14.68 daily assuming dosing at four separate times each day.

The manufacturer submitted a cost-utility analysis of cyclosporine 0.1% plus standard of care (SOC) compared with SOC in pediatric patients with VKC. SOC was defined as corticosteroid eye drop rescue medication and the use of over-the-counter lubricant eye drops. The analysis was conducted from the perspective of a Canadian publicly funded health care payer, with both costs and quality-adjusted life-years (QALYs) discounted at a rate of 1.5% per annum over a nine-year time horizon (i.e., until patients reached the end of adolescence, defined as 18 years of age).[3] The model structure was a Markov state transition model with three health states: symptomatic, asymptomatic, and death. Among the modelled patients, 55.4% were assumed to have perennial VKC and remained in the symptomatic health state; the remaining patients (with seasonal VKC) alternated between the symptomatic and asymptomatic health states every six months.[3] Patients had a monthly baseline risk of death. In the symptomatic health state, a constant proportion of patients were assumed to have treatment-emergent glaucoma.[3] The key clinical outcome in the model was the Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire score. Specifically, patients in the symptomatic health state accrued treatment-specific utility decrements based on mapping QUICK questionnaire VKC symptoms domain scores and daily activities domain scores as reported in the VErnal KeratoconjunctiviTIs Study (VEKTIS); a disutility was also associated with glaucoma. Direct medical costs were estimated from Canadian sources with the use of corticosteroids and eye drops based on the VEKTIS trial.[3]

In the manufacturer's base case, cyclosporine 0.1% plus SOC was associated with an incremental cost-utility ratio (ICUR) of $85,003 per QALY gained when compared with SOC alone. At a willingness-to-pay threshold of $50,000 per QALY, cyclosporine 0.1% plus SOC had a 0.03% probability of being cost-effective compared with SOC alone.[3]

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review identified several limitations with the manufacturer's model.

The manufacturer used a model structure that did not appropriately capture the clinical disease pathway. Although the model structure was described as containing "symptomatic" and "asymptomatic" health states, it did not adequately consider the clinically meaningful changes experienced by patients with severe VKC. Regardless of patients' responses to treatment, they would remain in the symptomatic health state for the duration in which symptoms are expected (e.g., six months for seasonal VKC and indefinitely for perennial VKC). Furthermore, the model did not explicitly capture aspects of VKC natural history, including the waxing and waning of symptoms over time, changes in the seasonality of the disease, and the potential resolution of disease symptoms as patients age. Further, the model structure did not reflect how costs may change with disease severity.

The manufacturer's model also did not consider relevant comparators within its analysis. The SOC modelled by the manufacturer did not include other immunomodulators (such as tacrolimus, reported by clinical experts consulted by CADTH to be an off-label steroid-sparing drug commonly used to manage severe VKC to avoid the risks associated with elevated intraocular pressure [IOP]). Consequently, the modelled SOC does not reflect current Canadian clinical practice, and the potential cost-effectiveness of cyclosporine 0.1% against such comparators is unknown.

Efficacy was modelled based on changes in QUICK questionnaire scores. However, due to the measurement properties of this scale and the imbalance between the treatment and control groups studied in the VEKTIS trial, the meaningfulness of the QUICK questionnaire scores as observed within the trial is limited. Furthermore, although the differences in QUICK questionnaire scores between treatment and control groups over the trial duration were available monthly (which would have aligned with the model's monthly cycle length), the manufacturer calculated and incorporated a four-month mean difference and set standard error arbitrarily at 10% of the mean — artificially increasing the precision of the efficacy estimates. In the manufacturer's model, a large magnitude of the QALY gains were accrued during the extrapolated period (0.40 QALYs) compared with the observed period (0.02 QALYs). However, as the clinical review concluded, the generalizability of the results noted from this trial to the Canadian clinical practice setting is unknown. Therefore, it remains unclear whether the modelled benefits would, in fact, be realized. Furthermore, the submitted model was unable to account for the potential impact of patients switching to alternative treatments over time due to unsatisfactory responses.

The manufacturer further used an unvalidated algorithm to map health utilities to two separate domains of the QUICK questionnaire: the VKC symptoms domain score and daily activities domain score. According to the clinical experts consulted by CADTH, these two domains are likely highly correlated. Consequently, the manufacturer's approach would likely double-count the impact of VKC treatment on health utilities. The clinical experts consulted by CADTH further expressed the opinion that there was limited face validity in the health states used to map utilities values to the two QUICK domains. The worst VKC

symptom score and worst daily activities score were assumed to be equivalent to the utility impacts associated with severe dry eyes and moderate depression, respectively. The clinical experts expressed the opinion that severe dry eye disease has less of an impact on quality of life than the worst VKC symptoms (described by QUICK questionnaire symptoms domain scores); and they were uncertain whether moderate depression would appropriately approximate the quality-of-life effects associated with the worst QUICK daily activities domain scores. The algorithm used by the manufacturer also assumed a linear relationship between health utilities and QUICK questionnaire scores without any supportive evidence. Collectively, these limitations regarding the accuracy of the estimated health benefits are of significant concern.

Although the manufacturer claimed to have modelled the treatment-emergent impacts of glaucoma by capturing the disutility of glaucoma, the probability and cost parameters more accurately reflected the incidence and management of elevated IOP, according to the clinical experts consulted by CADTH. The experts further indicated that there is no discernable health utility impact associated with elevated IOP. By applying a disutility associated with glaucoma as a proxy for elevated IOP, the manufacturer's approach favoured cyclosporine 0.1%. The manufacturer also included the cost of over-the-counter lubricant eye drops despite the fact that the majority of Canadian public drug plans do not cover their costs. Lastly, the manufacturer used an arbitrary assumption (5% or 10% of mean) to estimate the standard error for a significant proportion of model input parameters. Therefore, the cost-effectiveness results of the submitted model may not reflect the true uncertainty that would be associated with the model input parameters.

CADTH attempted to address some of the limitations by incorporating monthly efficacy parameters, removing the health utility impact of QUICK daily activities domain scores and of elevated IOP, and removing lubricant eye drop costs. Based on the CADTH reanalyses, the ICUR of cyclosporine 0.1% plus SOC compared with SOC alone was $356,474 per QALY.

Conclusions

Based on the parameters that CADTH could modify in the manufacturer's model, CADTH estimated that the ICUR of cyclosporine 0.1% plus SOC compared with SOC alone was $356,474 per QALY. At a willingness-to-pay threshold of $50,000 per QALY, cyclosporine 0.1% plus SOC was not cost-effective compared with SOC alone. A price reduction of more than 81% is required for cyclosporine 0.1% plus SOC to achieve an ICUR of less than $50,000 per QALY compared with SOC alone.

Considerable uncertainty remains in this analysis given the limitations with the model structure and the uncertainties in the clinical data based on VEKTIS. As noted in the clinical review, the generalizability of the findings from VEKTIS to Canadian clinical practice is unknown. Given that the majority of the benefits predicted in the economic model occur in the extrapolation period (for which limited long-term comparative clinical data are not available), careful consideration is required when interpreting the cost-effectiveness results. The cost-effectiveness of cyclosporine 0.1% compared with other relevant off-label comparators remains unknown.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a three-state Markov model to assess the cost-utility of cyclosporine plus standard of care (SOC) versus SOC alone in pediatric patients with severe vernal keratoconjunctivitis (VKC) (Figure 1, Appendix 4). SOC was defined as corticosteroid eye drops as rescue medication and use of over-the-counter (OTC) lubricant eye drops. The cost-utility analysis was conducted from the perspective of a Canadian publicly funded health care payer with monthly cycles until the end of adolescence; both costs and quality-adjusted life-years (QALYs) were discounted at a rate of 1.5% per annum.[3] Baseline patient characteristics were based on the VErnal KeratoconjunctiviTIs Study (VEKTIS) (mean age: 9 years; 78.6% male; 55.4% with perennial severe VKC; 44.6% with seasonal severe VKC).[3,4]

The three health states defined in the model were symptomatic ("on VKC treatment"), asymptomatic ("not on VKC treatment"), and death.[3] All patients entered the model in the symptomatic health state. Patients with perennial VKC remained in the symptomatic health state until death or until the end of the modelled time horizon, while patients with seasonal VKC alternated between the symptomatic and asymptomatic health states every six months until death or the end of the modelled time horizon. Patients had a monthly baseline risk of death. While in the symptomatic health state, a constant proportion of patients were assumed to have treatment-emergent glaucoma.[3]

Patients in the asymptomatic state were assumed to have the same health utility as the general Canadian population and not to incur any costs.[3] The key clinical outcome in the model was the Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire score. Patients in the symptomatic health state could accrue health utility decrements each month associated with the QUICK questionnaire VKC symptoms domain score and decreased daily activities domain score. A four-month average change in QUICK questionnaire score between the treatment group (cyclosporine 0.1% four times daily) and the control group, as reported in each arm of VEKTIS, was used to model the efficacy of cyclosporine 0.1% plus SOC over the entire model time horizon.[3] Utility values were mapped based on a linear function. The worst possible score (assuming out of 100%) in the symptoms domain was assumed to be equivalent to a utility decrement associated with severe dry eye disease; similarly, the worst possible score in the daily activities domain was assumed to be equivalent to a utility decrement associated with moderate depression. These utility decrements were determined separately for each domain and summed together to derive the treatment-specific and cycle-specific health state utility decrement. A utility decrement was further assumed in patients who experienced glaucoma.[3] Drug costs for cyclosporine 0.1% were provided by the manufacturer; the lowered twice-daily maintenance dose was not modelled.[3] The use of corticosteroid rescue medication and OTC lubricant eye drops was based on VEKTIS. Although dexamethasone 0.1% was the corticosteroid studied in VEKTIS,[5] the model assumed the cost of prednisolone 0.12% when modelling the cost of rescue medication.[3] The frequency of general practitioner and ophthalmologist visits and the proportion of patients requiring treatment for glaucoma (as a treatment-related adverse event) were based on clinician feedback. The unit cost of health care resources was derived mostly from provincial sources.[3,6,7]

Manufacturer's Base Case

The manufacturer's base-case results are presented in Table 2 (a detailed breakdown of the deterministic results is also presented in Table 13, Appendix 4). Cyclosporine 0.1% plus SOC was associated with 0.42 incremental QALYs at an additional cost of $35,394 compared with SOC alone, resulting in an incremental cost-utility ratio (ICUR) of $85,003 per QALY gained. At a willingness-to-pay threshold of $50,000 per QALY, cyclosporine 0.1% plus SOC had a 0.03% probability of being cost-effective compared with SOC alone (Figure 3, Appendix 4).

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

	Total Cost ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	Incremental Cost per QALY ($)
SOC	3,572		6.81		
Cyclosporine 0.1% + SOC	38,966	35,394	7.23	0.42	85,003

QALY = quality-adjusted life-year; SOC = standard of care.

Source: Manufacturer's pharmacoeconomic submission.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer explored a number of parameter and structural uncertainties through additional sensitivity analyses. The manufacturer reported that the model was robust to changes in discount rate, variation in the proportion of perennial and seasonal VKC, the assumed duration of seasonal VKC, and the frequency of physician visits. The results of the pharmacoeconomic model were found to be the most sensitive to changes in the QUICK questionnaire utility decrement values, the proportion of patients treated for glaucoma, and addition of the cost of a different cyclosporine formulation (ophthalmic emulsion, 0.05% weight by volume) for patients receiving only SOC.

The manufacturer also conducted a scenario analysis under a lifetime time horizon to explore the impact of treatment on a proportion of patients with reduced visual acuity in adulthood (due to VKC complications or adverse effects associated steroid use in childhood) or those who remained symptomatic of VKC. The manufacturer reported an ICUR of $8,959 per QALY gained under this scenario analysis.

Limitations of the Manufacturer's Submission

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

- **The model structure does not appropriately capture the clinical disease pathway**: An appropriate model structure for economic evaluation should capture relevant and meaningful underlying clinical or biological processes. The model submitted by the manufacturer consisted of three health states: symptomatic, asymptomatic, and death. Patients with perennial VKC at baseline remained in the symptomatic health state regardless of treatment efficacy; patients with seasonal VKC at baseline cycled between symptomatic and asymptomatic health states, although this was similarly not dependent on treatment efficacy. Therefore, transitions in the model were not dependent on the effectiveness of treatment. Rather, the effectiveness of treatment (with severity of the

disease) was captured within the health state by linking utilities to the trial-reported QUICK questionnaire scores.

- The manufacturer's model structure does not adequately consider the natural history of the disease or the link between disease severity and costs. The submitted model assumed that the proportion of patients with perennial and seasonal severe VKC would remain consistent throughout the modelled time horizon. This is inappropriate, because according to the clinical experts consulted by CADTH, symptoms of VKC wax and wane over time. Patients may have perennial VKC in one year but seasonal VKC in subsequent years; similarly, patients with seasonal VKC in one year may experience perennial VKC thereafter. Furthermore, the severity of the disease tends to wane during later years and is expected to resolve over time (i.e., with age) in a majority of patients. According to clinical experts consulted by CADTH, approximately 50% patients would still have VKC by 12 years of age, but only 10% would still have VKC by the end of adolescence. The manufacturer's submitted model did not capture any of these aspects of the condition nor how they would be affected by treatment.

  The manufacturer's submitted model was further unable to explicitly link health care costs to disease severity. The manufacturer instead assumed that resource use depended on treatment assignment. It would have been more appropriate to directly model how specific resource use and costs may vary as disease severity changes through the introduction of health states based on disease severity. CADTH was unable to address these limitations associated with the submitted model structure.
- **Missing relevant comparators**. The SOC modelled by the manufacturer only involved corticosteroid rescue medication and use of OTC lubricant eye drops. It did not include other relevant comparators, such as other immunomodulators. Consequently, the modelled SOC does not reflect current Canadian clinical practice in which off-label treatments are most commonly used to manage patients with this condition. Clinical experts consulted by CADTH stated that current treatment for patients with severe VKC involves the use of steroid-sparing drugs, such as tacrolimus, to avoid the risks associated with elevated intraocular pressure (IOP). Therefore, the manufacturer's submitted model was only able to address the cost-effectiveness of cyclosporine 0.1% with rescue medication compared with rescue medication use alone; it did not estimate the potential cost-effectiveness of cyclosporine 0.1% compared with other relevant off-label comparators that are more commonly used in Canadian practice. As a result, the potential cost-effectiveness of cyclosporine 0.1% versus other relevant comparators is uncertain.
- **Modelled comparative efficacy is uncertain**. The CADTH clinical report noted a number of issues that affect the comparability of the treatment and control groups studied in VEKTIS and the overall interpretability of the clinical inputs used to inform the economic model. The baseline characteristics in the trial were noted to be imbalanced, with patients randomized to the cyclosporine 0.1% four-times-daily treatment arm showing a tendency to have a more severe form of VKC. Furthermore, the proportions of patients who discontinued were found to be imbalanced between groups, with the lowest discontinuation rates observed in the cyclosporine 0.1% four-times-daily group. The CADTH clinical report concluded that the compounded impact of these limitations favour cyclosporine 0.1% four times daily and, as such, likely favours cyclosporine 0.1% as it is presently modelled in the manufacturer's economic model.

  The CADTH clinical report further identified a number of uncertainties associated with the meaningfulness of the QUICK questionnaire scores observed in VEKTIS. The QUICK questionnaire was originally developed and validated in Italian; evidence for its validity in

other languages has not been found. Lack of evidence regarding inter-rater and test-retest reliability and the responsiveness of QUICK questionnaire scores add further uncertainty to the meaningfulness of this measure. Furthermore, the minimal clinically important difference for QUICK questionnaire scores is unknown. Given these limitations, it is difficult to meaningfully interpret the QUICK questionnaire score results observed in VEKTIS.

VEKTIS reported the monthly change in QUICK questionnaire scores between the treatment group and the control group over the trial's duration;[4] yet the manufacturer calculated and applied the four-month average change in QUICK questionnaire score between the treatment group and control group for each domain within the model.[3] Furthermore, standard errors were arbitrarily assumed to be equivalent to 10% of the mean values.[3] Given that the model cycles are monthly, it would have been more appropriate to incorporate the monthly changes in the efficacy and standard errors values as observed in the trial rather than using a four-month mean value. This approach artificially increased the precision of the efficacy estimates used in the manufacturer's model.

- **Uncertain validity of long-term treatment effects**. The manufacturer applied the average clinical efficacy observed in the first four months of the VEKTIS trial over the modelled nine-year time horizon.[3] However, the majority of the clinical benefits estimated in the manufacturer's model (96%) occurred within the extrapolated period: 0.40 QALYs compared with 0.02 QALYs accrued in the observed period (Table 13). This finding is concerning because the long-term efficacy and safety of cyclosporine 0.1% is inconclusive, as noted in the CADTH clinical review. Results from the eight-month follow-up phase of VEKTIS have strong limitations due to lack of control, broken randomization, and self-selection. Furthermore, the submitted model was unable to account for the potential impact of patients switching to alternative treatments over time due to unsatisfactory responses. According to the clinical experts consulted by CADTH, clinicians administer different treatments until an effective treatment regimen is identified. Consequently, it is unlikely that the comparative efficacy observed in the controlled trial environment will persist in practice, because patients are ultimately administered other treatments that better control symptoms. CADTH was unable to address this limitation given the submitted model structure.

  Although the manufacturer submitted a lifetime model as an exploratory analysis (which would be relevant given the potential for this treatment to be used off-label in a small proportion [< 10%] of patients who may continue to experience VKC in adulthood), according to the clinical experts consulted by CADTH, the uncertainty associated with the long-term persistence of treatment effect — combined with the issues noted previously regarding model structure — render the manufacturer's lifetime time horizon scenario analysis highly uncertain. Furthermore, the only available comparative clinical evidence for cyclosporine 0.1% has been studied in a pediatric population; it is unclear whether the efficacy of cyclosporine 0.1% as observed in a pediatric population can be translated to an adult population. Consequently, CADTH reviewers did not explore this lifetime time horizon scenario in the CADTH reanalyses.

- **Inappropriate modelling of health utilities**. The manufacturer mapped health utilities to QUICK questionnaire scores, a disease-specific quality-of-life measure based on 16 items across two domains: VKC symptoms and daily activities.[3] As discussed previously, CADTH's clinical report noted limited validity, reliability, and responsiveness with this scale. Also, the potential correlation between the symptoms and daily activities domains were not explored in literature or by the manufacturer. According to the clinical experts

consulted by CADTH, VKC symptoms and daily activities are likely highly correlated in terms of their impact on a patient's quality of life. Consequently, the manufacturer's approach (adding the health utility decrements from each individual domain to calculate the disutility impact of treatment and disease) may risk double-counting the impacts on health utilities. CADTH reviewers addressed this limitation in the reanalyses.

Additional limitations with the approach were noted. Firstly, the manufacturer assumed that the maximum utility impact on the symptoms domain would be equivalent to severe dry eye disease, while the maximum utility impact on the daily activities domain would be equivalent to moderate depression. However, the relationship between the individual domains of the QUICK questionnaire score to these proxies (i.e., severe dry eye disease and moderate depression) is unclear. The clinical experts consulted by CADTH expressed the view that there is limited face validity with the use of these proxies. According to the clinical experts consulted, patients with the worst VKC symptoms would likely experience health states worse than severe dry eye disease; and it is uncertain whether moderate depression appropriately approximates the quality-of-life effects associated with the worst QUICK daily activities domain scores. Furthermore, the manufacturer used an unvalidated algorithm to map health utilities to QUICK questionnaire scores assuming a linear relationship (i.e., a change in the QUICK questionnaire score was assumed to reflect a proportionally equal change). This algorithm is unsubstantiated by any supportive evidence and adds uncertainty to the manufacturer's approach. Collectively, these limitations warrant significant concern regarding the predictive validity of the manufacturer's approach to modelling the health utility associated with severe VKC, as it remains uncertain whether the algorithm reflects the underlying relationship between disease and health utilities. This renders the cost-effectiveness results of the manufacturer's model substantially uncertain.

- **Inconsistent modelling of harms**. The manufacturer consulted clinical experts to elicit treatment-dependent probabilities of glaucoma for the model.[3] However, according to the clinical experts consulted by CADTH, glaucoma is a rare adverse event. In fact, no cases of glaucoma were reported in VEKTIS. According to the clinical experts consulted by CADTH, the probabilities assumed in the manufacturer's submission more appropriately reflect the risk of elevated IOP, which is unlikely to lead to glaucoma if identified and treated early. Furthermore, the costs assumed in the manufacturer's model to manage this treatment-emergent adverse event (i.e., timolol 0.25%) reflect the treatment most commonly offered in cases of elevated IOP. The clinical experts consulted by CADTH noted that there is no discernable health utility impact associated with elevated IOP and that elevated IOP is often caught early and managed accordingly. Therefore, it is inconsistent to apply the disutility associated with glaucoma to cases of elevated IOP within the model. This practice may be favourable for cyclosporine 0.1%. CADTH addressed this limitation in the reanalyses.
- **Inclusion of costs not covered by Canadian public plans**. The submitted model included OTC lubricant eye drops as costs, but the majority of Canadian public drug plans do not cover these medications. Because less lubricant use is attributed to cyclosporine 0.1%,[4] the manufacturer may have slightly overestimated the potential cost savings associated with cyclosporine 0.1%. CADTH addressed this limitation in the reanalyses.
- **Use of arbitrary coefficient of variation:** For a significant portion of input parameters within the manufacturer's model, the standard error was fixed to be 5% or 10% of the mean estimates. The arbitrary assumption to define probability distributions is inappropriate;[8] therefore, the uncertainty observed in the probabilistic results may not fully reflect the true uncertainty around model parameters.

CADTH Common Drug Review Reanalyses

Before undertaking any reanalyses, CADTH revised two aspects of the manufacturer's base case. Firstly, CADTH excluded the drug dispensing fees and mark-up costs that had been included in the model submitted by the manufacturer. Secondly, CADTH corrected an error in the manufacturer's model that allowed the QUICK daily activities domain score to decrease below a minimum score of zero, leading the associated utility decrement function to counterintuitively generate utility gains (Appendix 4).

Subsequently, CADTH conducted the following reanalyses of the revised manufacturer's base case to address the previously identified limitations:

- **Observed monthly mean QUICK questionnaire score parameters.** Monthly mean values and standard errors observed in the first four months of VEKTIS[4] were incorporated into the model in lieu of the four-month average QUICK questionnaire score and the assumed standard error of 10% of the mean QUICK questionnaire score.
- **Removal of health utility impact from QUICK questionnaire daily activities domain scores.** Change in QUICK daily activities domain scores was not assumed to be associated with health disutility.
- **Assuming no utility decrement from elevated IOP.** To remain consistent with the modelling of the treatment-emergent impacts of elevated IOP and the feedback from the clinical experts consulted by CADTH, elevated IOP was assumed not to be associated with a health utility decrement.
- **Removal of lubricant eye drop costs.** CADTH removed OTC lubricant eye drop costs, as these are not covered by public drug plans.

In the CADTH base case, consisting of reanalyses 1 to 4 in Table 3, cyclosporine 0.1% plus SOC was associated with 0.09 incremental QALYs at an additional cost of $32,060 compared with SOC alone, resulting in an ICUR of $356,474 per QALY gained (Table 3). At a willingness-to-pay threshold of $50,000 per QALY, cyclosporine 0.1% plus SOC had a 0.00% probability of being cost-effective compared with SOC. A price reduction of more than 81% is required for cyclosporine 0.1% plus SOC to achieve an ICUR of less than $50,000 per QALY compared with SOC alone.

Table 3: CADTH Reanalysis (Cyclosporine 0.1% Plus SOC Versus SOC)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY)
	Manufacturer's base case	Cyclosporine 0.1% + SOC	38,966	7.23	-
		SOC	3,572	6.81	-
		Incremental	*35,394*	*0.42*	85,003
	Revised manufacturer's base case[a]	Cyclosporine 0.1% + SOC	35,507	7.17	-
		SOC	3,465	6.81	-
		Incremental	*32,042*	*0.36*	89,128
1	Observed monthly mean QUICK questionnaire score parameters	Cyclosporine 0.1% + SOC	35,521	7.17	-
		SOC	3,467	6.81	-
		Incremental	*32,054*	*0.35*	90,306
2	Removal of health utility impact from QUICK daily activities domain scores	Cyclosporine 0.1% + SOC	35,529	7.21	-
		SOC	3,468	7.06	-
		Incremental	*32,061*	*0.15*	212,271
3		Cyclosporine 0.1% + SOC	35,509	7.23	-

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY)
	Assuming no utility decrement from elevated IOP	SOC	3,473	6.93	-
		Incremental	*32,036*	*0.30*	107,433
4	Removal of lubricant eye drop costs	Cyclosporine 0.1% + SOC	35,383	7.17	-
		SOC	3,345	6.81	-
		Incremental	*32,038*	*0.36*	89,275
CADTH Base Case					
	1 + 2 + 3 + 4	**Cyclosporine 0.1% + SOC**	**35,410**	**7.27**	**-**
		SOC	**3,350**	**7.18**	**-**
		Incremental	***32,060***	***0.09***	***356,474***

ICUR = incremental cost-utility ratio; IOP = intraocular pressure; QALY = quality-adjusted life-year; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; SOC = standard of care.

[a] Derived from the manufacturer's pharmacoeconomic submission that was corrected by CADTH. The manufacturer had submitted a model that included dispensing fees and mark-up costs (which are not considered as part of CADTH analyses) and had an error that allowed the QUICK questionnaire daily activities domain score to decrease below the minimum score of zero, leading the associated utility decrement to counterintuitively generate health utility gains.

Table 4: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

ICURs ($/QALY Gained) of Cyclosporine 0.1% Plus SOC Versus SOC Alone		
Price	**Revised Manufacturer's Base Case**	**Reanalysis by CDR**
Submitted	89,128	356,474
10% reduction	79,867	318,582
15% reduction	75,189	299,799
20% reduction	70,605	281,594
25% reduction	65,806	263,132
30% reduction	61,248	244,521
40% reduction	**51,793**	206,605
50% reduction	42,475	169,378
60% reduction	33,020	132,123
70% reduction	23,709	94,520
80% reduction	14,343	57,252
81% reduction	13,421	53,680
82% reduction	12,477	**49,870**

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Because the clinical experts consulted by CADTH indicated that the health utility decrement associated with the worst QUICK questionnaire score for VKC symptoms may be worse than that of severe dry eye disease (utility decrement of –0.120), CADTH reviewers conducted an additional scenario analysis that explored a larger health utility decrement value. This scenario analysis equated the worst VKC symptoms with the health utility decrement associated with moderate depression (utility decrement of –0.418) — a decrement that was associated with the worst QUICK questionnaire daily activities domain score in the manufacturer's submitted model. This increased the incremental QALYs attributable to cyclosporine 0.1% plus SOC compared with SOC alone, thereby reducing the ICUR to $157,267 per QALY gained (Table 14, Appendix 4).

CADTH also attempted to conduct subgroup analyses for patients with perennial VKC (Analysis S2a) and patients with seasonal VKC (Analysis S2b). However, the resulting

ICURs were similar, given the structure of the manufacturer's model (in which costs and efficacy are applied constantly, regardless of VKC type) (Table 14, Appendix 4). For a similar reason, it was not possible to conduct scenario analyses to explore the potential cost-effectiveness of cyclosporine 0.1% by patient baseline age.

Issues for Consideration

- Because VKC is a climate-sensitive condition, Canadian clinicians may practice different frequency of disease monitoring depending on geographic location and accessibility of health care.
- Feedback from the clinical experts consulted by CADTH indicated that patients may be receiving compounded cyclosporine ophthalmic emulsion for severe VKC through hospitals or compounding pharmacies. As per the Health Canada guideline, "compounding should only be done if there is a therapeutic need or lack of product availability and should not be done solely for economic reasons for the health care professionals."[9] Given the availability of cyclosporine 0.1%, compounded cyclosporine should not be used, justifying its exclusion as a comparator. Variable formulations of cyclosporine ophthalmic emulsion may remain available through compounding pharmacies. However, the clinical experts consulted by CADTH reported variability in quality, efficacy, cost, and patient access with compounded formulations.
- Although the treatment regimen recommended by Health Canada is administration four times daily, the treatment can be maintained at the decreased dose of one drop twice daily once adequate control of signs and symptoms is achieved.[2] This dose decrease was not modelled in the manufacturer's pharmacoeconomic submission, leading to a more conservative cost-effectiveness estimate of cyclosporine 0.1%.
- According to the clinical experts consulted by CADTH, compliance among the pediatric population is an issue, especially when cyclosporine takes longer than steroids to take effect. Compliance is not explicitly captured in the manufacturer's model.
- According to the clinical experts consulted by CADTH, cyclosporine 0.1% may be used off-label for treatment beyond adolescence in adult patients with VKC.
- Although cyclosporine 0.1% is supplied in single-use vials, patients may consider reusing the vials to prolong treatment. According to the clinical experts consulted by CADTH, the practice of reusing vials has been observed with other ophthalmic treatments not covered by public drug plans when cost is an issue for patients.

Patient Input

Input was received from Canadian Organization for Rare Disorders based on interviews with four clinicians (two pediatric ophthalmologists and two optometrists) and 10 families who have children diagnosed with severe VKC. Most families reported seasonal symptoms that appear in spring and last five to eight months, similar to the manufacturer's assumption that the duration of seasonal VKC symptoms would be six months. Symptoms were reported to include red eyes, puffiness, itching, and blurry vision; these symptoms interfered with the children's and families' abilities to participate in social and recreational activities. These descriptions of VKC symptoms and their impacts on daily activities appear to be similar in content to the items in the QUICK questionnaire. Family input revealed the potential for severe VKC to ameliorate over time. Such gradual improvement in severe VKC symptoms was not modelled in the manufacturer's pharmacoeconomic model.

Regarding currently available treatments, many families reported experience with several treatment regimens taken in sequence or concomitantly. In particular, patients reported the use of other immunomodulator eye drops, including tacrolimus and other cyclosporine formulations, such as Restasis (cyclosporine 0.05%). The manufacturer's model did not evaluate any of these treatments.

Conclusions

Given the parameters that CADTH could modify in the manufacturer's model, CADTH estimated that the ICUR of cyclosporine 0.1% plus SOC compared with SOC alone was $356,474 per QALY. At a willingness-to-pay threshold of $50,000 per QALY, cyclosporine 0.1% plus SOC was not cost-effective compared with SOC alone. A price reduction of more than 81% is required for cyclosporine 0.1% plus SOC to achieve an ICUR of less than $50,000 per QALY compared with SOC alone.

Considerable uncertainty remains in this analysis given the limitations with the model structure and the uncertainties in the clinical data based on VEKTIS. As noted in the clinical review, the generalizability of the findings from VEKTIS to Canadian clinical practice is unknown. Given that the majority of the benefits predicted in the economic model occur during the extrapolation period (for which limited long-term comparative clinical data are not available), careful consideration is required when interpreting the cost-effectiveness results. The cost-effectiveness of cyclosporine 0.1% compared with other relevant off-label comparators remains unknown.

Appendix 1: Cost Comparison

The comparators presented in Table 5 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: CDR Cost Comparison Table for Treatments Indicated for Pediatric Severe VKC

Drug/Comparator	Dosage Form	Size	Price ($)	Recommended Dose	Average Daily Drug Cost ($)
Cyclosporine 0.1% (Verkazia)	Ophthalmic emulsion	0.3 mL single-dose vials	$110.0000 per 30- pack[a]	1 drop into affected eye(s) 4 times daily	14.68

CDR = CADTH Common Drug Review; VKC = vernal keratoconjunctivitis.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2019) unless otherwise indicated, and do not include dispensing fees. One millilitre is assumed to contain 20 drops. Both eyes are assumed to be treated.

[a] Manufacturer's submitted price. Each single-dose unit is enough to treat both eyes.

Table 6: CDR Cost Comparison Table for Drugs (Ophthalmic Solutions and Suspensions) Used Off-Label for Pediatric Severe VKC

Drug/Comparator	Dosage Form	Size	Price Per Unit ($)	Recommended Dose	Average Daily Drug Cost ($)
Mast-Cell Stabilizers					
Lodoxamide 0.1% (Alomide)	Ophthalmic solution	10 mL	1.2650	1 to 2 drops into affected eye(s) 4 times daily	0.51 to 1.01
Sodium cromoglycate 2% (Opticrom, generics)	Ophthalmic solution	10 mL	0.9500	2 drops into affected eye(s) 4 times daily	0.76
Dual-Activity Antihistamines/Mast-Cell Stabilizers					
Bepotastine besilate 1.5% (Bepreve)	Ophthalmic solution	5 mL 10 mL	5.9740[c]	1 drop into affected eye(s) twice daily	1.19
Ketotifen 0.025% (Zaditor, generics)	Ophthalmic solution	5 mL	5.2920[c]	1 drop into affected eye(s) once daily	0.53
Olopatadine 0.1% (Patanol, generics)	Ophthalmic solution	5 mL 10 mL 15 mL	2.1720[c]	1 drop into affected eye(s) twice daily	0.43
Olopatadine 0.2% (Pataday, generics)	Ophthalmic solution	2.5 mL	10.4520[c]	1 drop into affected eye(s) once daily	1.05
Olopatadine 0.7% (Pazeo)	Ophthalmic solution	2.5 mL	12.4080[c]	1 drop into affected eye(s) once daily	1.24
Steroids					
Dexamethasone 0.1% (Maxidex, generics)	Ophthalmic suspension	5 mL	1.7900	1 to 2 drops to affected eye(s) 4 to 24 times daily	0.716 to 8.592
Fluorometholone acetate 0.1% (FML, generic)	Ophthalmic suspension	5 mL 10 mL	3.4018	1 to 2 drops into affected eye(s) 2 to 4 times daily	0.68 to 2.72

Drug/Comparator	Dosage Form	Size	Price Per Unit ($)	Recommended Dose	Average Daily Drug Cost ($)
Fluorometholone acetate 0.1% (Flarex, generic)	Ophthalmic suspension	5 mL	2.0240	1 to 2 drops into affected eye(s) 2 to 4 times daily	0.40 to 1.62
Loteprednol etabonate 0.2% (Alrex)	Ophthalmic suspension	5 mL 10 mL	5.7280[c]	1 drop into affected eye(s) 4 times daily	2.29
Loteprednol etabonate 0.5% (Lotemax)	Ophthalmic suspension	2.5 mL 5 mL 10 mL 15 mL	4.4000[c]	1 to 2 drops into affected eye(s) 4 times daily	1.76 to 3.52
Prednisolone acetate 1% (Pred Forte, generics)	Ophthalmic suspension	5 mL 10 mL	1.9400	1 to 2 drops of affected eye(s) 2 to 4 times daily	0.39 to 1.55

CDR = CADTH Common Drug Review; VKC = vernal keratoconjunctivitis.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed July 2019)[10] unless otherwise indicated, and do not include dispensing fees. One millilitre is assumed to contain 20 drops. Both eyes are assumed to be treated.

[a] Prokopich et al., (2018).[11]

[b] Association québécoise des pharmaciens propriétaires price based on IQVIA DeltaPA database (July 2019).[12]

[c] Wholesale acquisition price based on IQVIA DeltaPA database (July 2019).[12]

Table 7: CDR Cost Comparison Table for Drugs (Gel and Ointments) Used Off-Label for Pediatric Severe VKC

Drug/Comparator	Dosage Form	Size	Price per Unit ($)	Recommended Dose
Immunomodulator				
Tacrolimus, 0.03% (Protopic)	Ointment	30 g 60 g 100 g	2.3740[a]	Apply to affected eye(s) 2 times daily
Tacrolimus, 0.1% (Protopic)	Ointment	30 g 60 g 100 g	2.5397[a]	Apply to affected eye(s) 2 times daily
Steroid				
Loteprednol etabonate 0.5% (Lotemax)	Ophthalmic gel	5 g	4.4320[b]	1 to 2 drops into affected eye(s) 4 times daily
	Ophthalmic ointment	3 g	6.4743[b]	Apply to affected eye(s) 4 times daily

CDR = CADTH Common Drug Review; VKC = vernal keratoconjunctivitis.

[a] Alberta Interactive Drug Benefit List (July 2019).[13]

[b] Wholesale acquisition price based on IQVIA DeltaPA database (July 2019).[12]

Appendix 2: Additional Information

Table 8: 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”	None		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Authors’ Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review

☐ 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

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

The cost-effectiveness of cyclosporine 0.1% (Verkazia) for severe vernal keratoconjunctivitis in children from four years of age through adolescence has been assessed by the Scottish Medicines Consortium[14] and the All Wales Medicines Strategy Group.[15,16] These reviews are summarized in Table 10.

Table 10: Health Technology Assessment Findings: SMC and AWMSG

	SMC (November 2018)[14]	AWMSG (2019)[15,16]
Treatment	Cyclosporine 1 mg/mL (0.1%) eye drops emulsion (Verkazia)	
Price	£227.93 per month (£1.00 = C$1.74; November 2018)	Redacted
Similarities with CDR submission	• Public health payer perspective • Markov model with symptomatic and asymptomatic health states. Patients transition between these health states if they have seasonal VKC. Patients begin at nine years of age and are followed over a nine-year time horizon, with monthly cycles. • Usage of rescue medication (i.e., course of topical corticosteroids four times daily for five days) based on VEKTIS trial	
Differences with CDR submission	• CMA was submitted • Ikervis and other cyclosporine ophthalmic emulsions were available as weighted comparators	
	• Duration of seasonal VKC was 5 months • Long-term model included; however, < 1% of patients remained in model after 18 years • Scottish and European resource use and cost parameters • No adverse event costs	• Welsh and European resource use and cost parameters
Manufacturer's results	• Incremental savings of £4,367 per patient over a nine-year time horizon associated with Verkazia	• Incremental savings of £5,033 per patient over a nine-year time horizon associated with Verkazia
Issues noted by the review group	• Comparable efficacy assumptions in the CMA are not supported by robust clinical data. However, the committee was reassured that Verkazia and Ikervis contain the same formulation of cyclosporine and that, as a result, comparable efficacy between these treatments is a reasonable assumption. • Several comparators within the weighted average basket may not be appropriate to include (i.e., Restasis and a special manufactured preparation of cyclosporine).	• CMA is inappropriate due to lack of well-designed equivalence and appropriate head-to-head trials.
Results of reanalyses by review group	• NA	• The most plausible cost savings are considered to range between £1,254 to £11,613, given that these estimates take into account the uncertainty surrounding the model inputs.
Recommendation	Accepted for use by NHS Scotland	Recommended as an option for use by NHS Wales

AWMSG = All Wales Medicines Strategy Group; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; NA = not available; NHS = National Health Service; SMC = Scottish Medicines Consortium; VEKTIS = VErnal KeratoconjunctiviTIs Study; VKC = vernal keratoconjunctivitis.

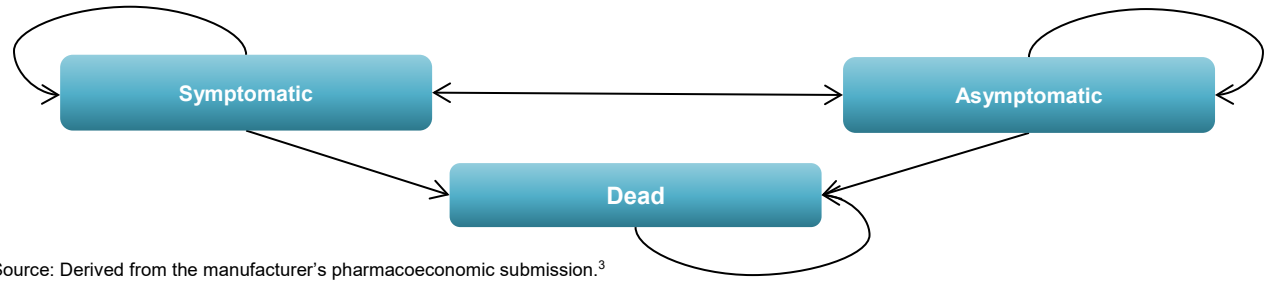
Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a three-state Markov model to assess the cost-utility of cyclosporine 0.1% plus standard of care to standard of care alone in pediatric patients with severe vernal keratoconjunctivitis (VKC) (Figure 1).[3] Baseline patient characteristics were based on the VErnal KeratoconjunctiviTIs Study (mean age: 9 years; 78.6% male; 55.4% perennial severe VKC; 44.6% seasonal severe VKC). All patients entered the model in the symptomatic health state and were followed over the next nine years, until they reached adolescence (age 18 years). Patients with perennial VKC remained in the symptomatic health state until death, while patients with seasonal VKC alternated between the symptomatic and asymptomatic health states every six months until death.

The manufacturer also modelled long-term costs and consequences in a scenario analysis over a lifetime time horizon (91 years, until the age of 100 years).

Figure 1: Manufacturer's Base-Case Model Structure



Source: Derived from the manufacturer's pharmacoeconomic submission.[3]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Baseline age and sex profile of patients and proportion of seasonal and perennial disease reflected the manufacturer's trial.[4]	Acceptable, according to the clinical experts consulted by CADTH. The experts also noted that the variation in climate across Canada may affect the actual proportion of patients with seasonal or perennial disease.
Efficacy	Based on VEKTIS data.[4] Note: Efficacy was based on the average difference in QUICK questionnaire scores over the first four months of VEKTIS.	The CADTH clinical report noted a number of issues associated with VEKTIS that affect its overall clinical significance and concerns regarding the validity and reproducibility of QUICK questionnaire. The manufacturer's application of the average score difference over the entire time horizon was inappropriate, as discussed in the main report. Furthermore, this was used to extrapolate beyond the observed trial period, which is not based on epidemiological studies. It is uncertain whether the average treatment effect observed over the four months of VEKTIS will persist for years.

Data Input	Description of Data Source	Comment
		Treatment options change based on patient response, so it is unlikely that the efficacy observed in the controlled trial environment will persist in practice, where patients are ultimately administered other treatments that better control symptoms.
Natural history	The probability of patients requiring glaucoma treatment was based on the manufacturer's consultation with Canadian clinical experts.[3]	According to the clinical expert consulted by CADTH, the probabilities of patients requiring glaucoma treatment used by the manufacturer more appropriately reflect the probabilities of treated patients who develop elevated IOP.
Health state utilities	Asymptomatic VKC: age and gender-specific general Canadian mean utility values and standard errors were derived from HUI3 values from Guertin et al., 2018.[17]	Inappropriate. As Guertin et al., 2018 recruited Canadians aged 12 and older, it is unclear whether the proportion of the HC–indicated population with ages below 12 years would have similar health utility preferences. Furthermore, although the lowest age group reported by the study was 12 years to 19 years, the manufacturer merged the utilities into an aggregate age group that reflects the results from ages 12 years to 25 years. However, these inputs are not expected to significantly affect the model.
	Symptomatic VKC: disutilities based on QUICK questionnaire symptoms domain scores and daily activities domain scores applied to general Canadian health state utility values. QUICK symptoms domain scores were mapped to utility values, with the maximum utility decrement set to those with severe dry eye disease as proxy (based on TTO values from Schiffman et al., 2003).[18] QUICK questionnaire daily activities domain scores were mapped to utility values, with the maximum utility decrement set to those with moderate depression as proxy (based on EQ-5D values from Sapin et al., 2004).[19]	Inappropriate. See main report. The generalizability of the manufacturer's utility values is further unclear because the values were sourced from adult populations whose demographic and epidemiologic characteristics may be different from the HC–indicated population. Multiple health utility instruments (i.e., HUI3, TTO, EQ-5D) were also used. Consistency with respect to the data used to estimate utility value is strongly recommended (i.e., same instrument, same population).[8]
Adverse event utilities Glaucoma	The utility decrement associated with glaucoma was based on HUI3 values from Wolfram et al., 2013.[20]	Inappropriate. The manufacturer used probability of glaucoma treatment that reflected the proportion of treated patients with elevated IOP instead. According to the clinical expert consulted for this review, elevated IOP is often asymptomatic, and is not expected to have an impact on patient utility, especially if managed.
Mortality	Age- and sex-specific mortality probabilities were based on the 2014 to 2016 life table from Statistics Canada.[21]	Acceptable. Although a more recent life table is available, updated mortality data did not

Data Input	Description of Data Source	Comment
		seem to significantly affect cost-effectiveness results.
Resource use and costs		
Drug cost	The cost of Verkazia was based on manufacturer's submitted price.[3] The costs of other drugs were based on the Ontario Drug Benefit Formulary.[7] A dispensing fee of $8.83 and pharmacy mark-up of 8% were applied based on the 2018 Canadian Association for Pharmacy Distribution Management Guidebook.	Appropriate. Appropriate. Mark-up and dispensing fees are not considered in CADTH reanalyses. They were excluded from the CADTH base case and all scenario analyses.
Medical procedures	Unit costs for medical procedures were based on the Ontario schedule of benefits.[6] Treatment-specific monitoring resource uses for general practitioner and ophthalmologist visits were based on the manufacturer's consultation with Canadian clinical experts.[3]	Appropriate. Inappropriate. According to the clinical experts consulted by CADTH, the frequency of visits has no direct correlation with the type of medication; it is based on disease severity and patient need. There is variability in monitoring practices in Canada, although clinical experts noted that general physicians do not generally manage VKC. Overall, the manufacturer's assumptions about resource use favour cyclosporine 0.1%, given that four times less resource use was assumed with cyclosporine 0.1% plus SOC compared with SOC alone. However, the number of clinician visits did not seem to significantly affect the cost-effectiveness results.
Symptomatic health state	Treatment-dependent monthly rescue medication utilization, eye drop utilization, and monitoring costs were based on VEKTIS.[4]	Uncertain. The extent to which resource use from VEKTIS (an international study) reflects Canadian practice is unclear. Although duration of rescue medication use is expected to be longer, according to the clinical experts consulted by CADTH, this would not affect costs because prescription cost captured wastage (i.e., a bottle of prednisone was assumed to be thrown out after a month).

EQ-5D = EuroQol 5-Dimensions questionnaire; HC = Health Canada; HUI3 = Health Utilities Index Mark 3; IOP = intraocular pressure; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; SOC = standard of care; TTO = time trade off; VEKTIS = VErnal KeratoconjunctiviTIs Study; VKC = vernal keratoconjunctivitis.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
SOC consists of the use of corticosteroid rescue medication and lubricants.	Inappropriate. Other off-label immunomodulators are available in Canada. A comparison with other steroid-sparing drugs (e.g., cyclosporine 0.1% plus SOC vs. immunomodulator plus SOC) would have been more appropriate, given that the clinical experts consulted by CADTH noted that current SOC involves the use of these off-label treatments. See main report.
Dexamethasone 0.1% eye drops were used as rescue therapy in VEKTIS,[5] but the model used the cost of prednisolone 0.12%.[3]	Inappropriate, but unlikely to have an impact on the model because the costs of both drugs are similar. According to the clinical experts consulted by CADTH, dexamethasone is most commonly prescribed.
The manufacturer's model sufficiently captured the experience of patients with severe VKC.	Inappropriate. The manufacturer did not capture the natural history of the disease (i.e., changes in severity over time). The manufacturer also did not explicitly link disease severity and cost.
The nine-year time horizon (i.e., until the end of adolescence at 18 years of age) sufficiently captures the costs and consequences relevant to the decision problem associated with Verkazia for the treatment of severe VKC in children between 4 years of age and adolescence.	Uncertain. Lifelong consequences associated with reduced visual acuity are not captured within the model, given the shorter time horizon. Although the manufacturer submitted an exploratory lifetime model, it was based on assumptions and extrapolated four-month VEKTIS evidence, increasing the uncertainty of extrapolation.
Seasonal patients were assumed to be symptomatic for six months and asymptomatic for six months every year.	Uncertain. According to the clinical expert consulted by CADTH, symptoms wax and wane over the years; the duration of VKC symptoms may change as patients age. Patient inputs received by CADTH indicated that seasonal VKC symptoms could last between five and eight months in a given year.
Although VKC may resolve in adulthood, the proportions of severe VKC patients with perennial or seasonal symptoms were constant. This effectively assumes that patients with perennial VKC at baseline will continue to suffer from perennial VKC over the modelled time horizon.	Inappropriate. According to the clinical expert consulted by CADTH, disease tends to wane with increased age, such that approximately 50% of patients would have VKC by age 12 while only 10% would have it by the end of adolescence.
Medication costs were adjusted by relative dose intensity (96.5%)[4] except for the cost of rescue corticosteroid medication.	Uncertain. The adherence rate does not necessarily indicate prescription fill rate. Given the public health care payer perspective, high rate of adherence, and potential for wasted eye drops, it is unclear whether eye drop prescriptions would reflect the trial's adherence levels.

SOC = standard of care; VEKTIS = VErnal KeratoconjunctiviTIs Study; VKC = vernal keratoconjunctivitis; vs. = versus.

Table 13: Summary of Results of the Manufacturer's Deterministic Base Case

	Deterministic Results		
	Cyclosporine 0.1% Plus SOC	SOC	Difference
Total costs ($)	**38,936**	**3,574**	**35,362**
Drug costs[a]	37,186	304	36,882
Monitoring costs	1,750	3,270	–1,520
Total QALYs	**7.14**	**6.72**	**0.42**
Observed period[b]	0.20	0.18	0.02
Extrapolated period[b]	6.94	6.54	0.40
ICUR ($/QALY gained)			**84,880**

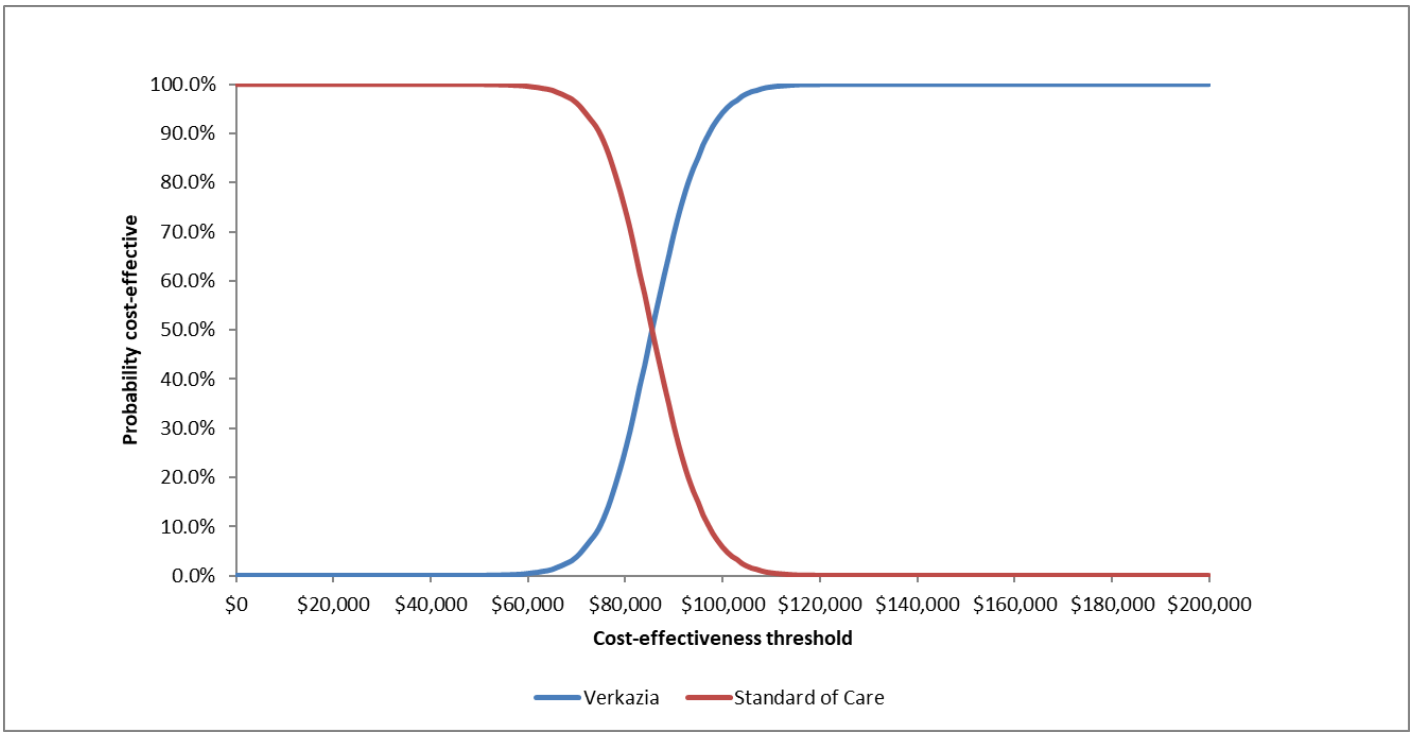
ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

[a] Includes the costs of cyclosporine 0.1%, rescue corticosteroid treatment, lubricant eye drops, and glaucoma treatment.

[b] The observed period represents the four-month randomized trial duration of VEKTIS. The extrapolated period represents the rest of the time horizon beyond the first four months.

Source: Manufacturer's pharmacoeconomic submission.[3]

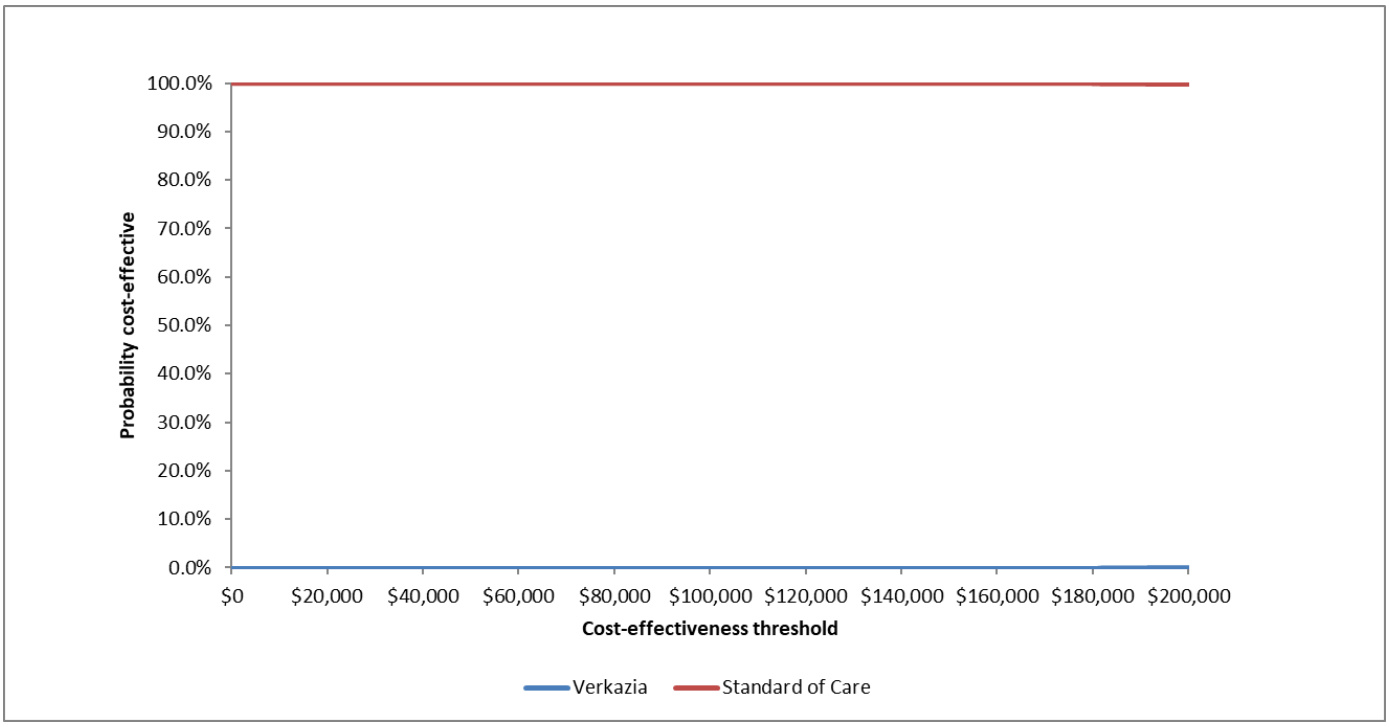
Figure 2: Manufacturer's Base-Case Cost-Effectiveness Acceptability Curve



Source: Manufacturer's pharmacoeconomic submission.[3]

CADTH Common Drug Review Reanalyses

Figure 3: CADTH Base-Case Cost-Effectiveness Acceptability Curve



CADTH conducted the following additional scenario and subgroup analyses:

Scenario analysis:

S1: The health utility decrement associated with the maximum Quality of Life in Children with Vernal Keratoconjunctivitis questionnaire VKC symptoms domain score (i.e., 100%) was assumed to be equivalent to moderate depression (mean: –0.418) instead of severe dry eye disease (mean: –0.120).

Subgroup analyses

S2a: Severe perennial VKC patients

S2b: Severe seasonal VKC patients

The results of these additional analyses are reported in Table 14.

Table 14: CADTH Scenario Analysis and Subgroup Analyses (Cyclosporine 0.1% Plus SOC Versus SOC)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY)
Scenario Analysis					
S1	Health utility decrement associated with the maximum QUICK questionnaire VKC symptoms domain score assumed equivalent to the moderate depression health state	Cyclosporine 0.1% + SOC	35,428	7.38	-
		SOC	3,346	7.17	-
		Incremental	32,082	0.20	157,267
Subgroup Analyses					
S2a	Severe perennial VKC	Cyclosporine 0.1% + SOC	45,375	7.26	-
		SOC	4,294	7.14	-
		Incremental	41,082	0.12	356,156
S2b	Severe seasonal VKC	Cyclosporine 0.1% + SOC	22,994	7.29	-
		SOC	2,178	7.24	-
		Incremental	20,816	0.06	354,987

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; SOC = standard of care; VKC = vernal keratoconjunctivitis.

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