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CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**Cyclosporine 0.1% (VERKAZIA — SANTEN CANADA INC.)**
Indication: Treatment of severe vernal keratoconjunctivitis in children from 4 years of age through adolescence.

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee recommends that cyclosporine 0.1% be reimbursed for the treatment of severe vernal keratoconjunctivitis (VKC) in children from four years of age through adolescence only if the following conditions are met.

**Conditions for Reimbursement**
**Initiation Criteria**
1. Between four and 18 years of age, inclusive.
2. Diagnosis of severe VKC defined as either:
   2.1. grade 3 (severe) or 4 (very severe) on the Bonini scale, OR
   2.2. grade 4 (marked) or 5 (severe) on the modified Oxford scale.
3. Severity of signs and symptoms of VKC should be documented by the treating physician at treatment initiation.
4. Patients previously treated with cyclosporine 0.1% but who discontinued treatment upon resolution of VKC signs and symptoms are eligible to reinitiate treatment if signs and symptoms of severe VKC recur and they meet the first and second initiation criteria.

**Discontinuation Criteria**
1. Treatment should be discontinued if no improvement in signs and symptoms of VKC is observed after four months of treatment.
2. Treatment should be discontinued once signs and symptoms of VKC have been resolved.

**Prescribing Conditions**
1. Patient must be under the care of a specialist physician with experience in the diagnosis and management of VKC.

**Pricing Conditions**
1. Reduced price.


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The CADTH Canadian Drug Expert Committee (CDEC) recommends that cyclosporine 0.1% be reimbursed for the treatment of severe vernal keratoconjunctivitis (VKC) in children from four years of age through adolescence only if the following conditions are met.

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**Discontinuation Criteria**

1. Treatment should be discontinued if no improvement in signs and symptoms of VKC is observed after four months of treatment.
2. Treatment should be discontinued once signs and symptoms of VKC have been resolved.

**Prescribing Conditions**

1. Patient must be under the care of a specialist physician with experience in the diagnosis and management of VKC.

**Pricing Conditions**

1. Reduced price.

## Reasons for the Recommendation

1. One double-masked, placebo-controlled, phase III randomized controlled trial (RCT) (VEKTIS) included children four to 18 years of age with severe VKC defined as grade 3 or 4 on the Bonini scale, grade 4 or 5 on the modified Oxford scale, and a mean score of four subjective symptoms (photophobia, tearing, itching, and mucous discharge) of 60 mm or greater using a 100 mm Visual Analogue Scale (VAS). The study showed that cyclosporine 0.1% administered four times daily was statistically significantly better than placebo in terms of the VEKTIS primary composite efficacy outcome (corneal fluorescent staining [CFS] penalized by rescue medication and the development of corneal ulcerations; between-groups difference in the least squares [LS] mean of 0.76 [95% confidence interval (CI), 0.26 to 1.27, $P = 0.007$]). Compared with placebo, patients treated with cyclosporine 0.1% four times daily demonstrated improvements on the average of four VAS symptoms measurements (LS mean difference, –19.411; 95%CI, –29.307 to –9.515) and health-related quality of life (HRQoL) as measured by the symptoms domain of the QUICK questionnaire (LS mean difference, –8.766; 95% CI, –16.403 to –1.129, $P = 0.049$). The proportion of the responders in the cyclosporine 0.1% four times daily treatment group was higher than in the placebo group (57.1% compared with 34.5%, respectively). No specific safety issues were identified with cyclosporine 0.1% use.
2. A CADTH Common Drug Review (CDR) reanalysis of the sponsor's cost-utility analysis suggests an incremental cost-utility ratio (ICUR) of $356,474 per quality-adjusted life-year (QALY) gained for cyclosporine 0.1% plus standard of care (SOC) compared with SOC alone (corticosteroid eye drops as rescue medication and/or lubricant eye drops) for the treatment of

severe VKC in children four to 18 years of age. A price reduction of more than 81% is required for cyclosporine 0.1% to be considered cost-effective at a $50,000 per QALY willingness-to-pay threshold.

## Discussion Points

- There is no evidence to suggest that cyclosporine 0.1% would benefit patients outside of the VEKTIS study population (e.g., patients with moderate VKC, patients who are asymptomatic, patients who are pre-symptomatic, or those older than 18 years of age).
- There is no evidence to support the combined use of cyclosporine 0.1% with the use of corticosteroids in patients with severe VKC. In the VEKTIS study, all patients were required to discontinue any topical or systemic corticosteroids prior to participation in the study. However, rescue medication with dexamethasone was permitted and consisted of one drop of 0.1% dexamethasone four times daily for a maximum of five consecutive days. No add-on chronic corticosteroid medication was offered to patients.
- The adherence rates in the VEKTIS study were higher than anticipated in clinical practice. The impact of poor adherence on the efficacy of cyclosporine 0.1% is unknown.
- A reduced dose frequency of cyclosporine 0.1% twice daily may be used as maintenance therapy according to the Health Canada product monograph. However, there is no clinical evidence included in the CADTH systematic review that evaluated the efficacy of switching from cyclosporine four times daily to twice daily in patients with severe VKC.
- The committee considered that, with Health Canada's granting of a Notice of Compliance to Verkazia, compounded cyclosporine 0.1% ophthalmic drops may no longer be available.

## Background

Cyclosporine 0.1% topical ophthalmic emulsion has a Health Canada indication for the treatment of severe VKC in children from four years of age through adolescence. It is available as a topical ophthalmic emulsion and the Health Canada–approved treatment regimen is administration four times daily. However, maintenance therapy can be given twice daily.

## Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CDR: a systematic review of published and unpublished phase III and IV RCTs of cyclosporine 0.1% topical ophthalmic emulsion and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a panel of clinical experts with experience treating patients with VKC, and patient group–submitted information about outcomes and issues important to patients.

### Summary of Patient Input

One patient group, the Canadian Organization for Rare Disorders (CORD), provided input for this submission. Patient perspectives were obtained from 10 semi-structured interviews with patient families who had a child diagnosed with severe VKC. The following is a summary of key input from the perspective of the patient group:

- Patients suffer from a range of symptoms, including itchiness, red eye, pain, and blurry vision. These symptoms are commonly seasonal, starting around springtime and lasting between five and eight months, but can be perennial.
- Symptoms interfere with the child's participation in school, in sports, in family events, and in every aspect of daily living. Parents reported that there was also a heavy impact on the entire family, not just the time spent in care, going to medical appointments, and daily administration of medicines, but also in regard to the ability to take part in many social and recreational activities.
- Parents reported having used a wide variety of therapies — antihistamines, lubricants, mast cell stabilizers, steroids, and immunosuppressants. Most also had experience with using cyclosporine in varying doses (including a commercial formulation and pharmacy compounded formulations).
- Parents want a treatment that reduces any potential long-term harm to their child's eyes as well as one that manages VKC symptoms on a reliable day-to-day basis.

## Clinical Trials

The systematic review included one double-masked, triple-arm, parallel-group, phase III RCT. The Vernal Keratoconjunctivitis Study (VEKTIS) (N = 169) included patients with a diagnosis of severe VKC defined as grade 3 (severe) or 4 (very severe) on the Bonini scale, a score on the modified Oxford scale of grade 4 (marked) or 5 (severe), and a mean score of four subjective symptoms (photophobia, tearing, itching, and mucous discharge) of 60 mm or greater using a 100 mm VAS. Patients aged four to 18 years with severe VKC were randomized in a 1:1:1 ratio to one of two cyclosporine 0.1% groups (four times daily or twice daily), or to placebo, both as topical ophthalmic applications. Patients received the study treatment for four months, at which point the primary outcome was assessed. Patients in the four times daily treatment group had the lowest proportion of discontinuation (10%), followed by the placebo group (15.8%), and the twice daily group (20%). A follow-up safety period of eight months was initiated after the four-month study period was concluded.

The lack of evidence versus an active comparator as defined in the systematic review protocol and the imbalance in the discontinuation rate between treatment groups are noted limitations.

## Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- Response to treatment and improvement in ocular surface: Reported by the VEKTIS primary composite efficacy outcome of the difference from baseline in CFS score at assessment visit adjusted through penalties based on the use of rescue medication and the development of corneal ulcerations. A positive value in the patient composite efficacy score indicated improvement. Other outcomes related to response to treatment and improvement in ocular surface included the outcomes of CFS responders and the use of rescue medication. No evidence was found for the validity, reliability, responsiveness, or minimum important difference of the composite primary end point. This end point takes into consideration signs (keratitis as assessed by the corneal staining score), symptoms (as rescue therapy would be used for worsening symptoms), and the use of corticosteroids, which are associated with harms in patients with VKC.
- HRQoL: Reported by the QUICK questionnaire, a self-reported questionnaire for measuring HRQoL in children from five to 12 years of age with allergic conjunctivitis, keratoconjunctivitis, or both. The questionnaire is composed of 16 items in two domains — 12 items in the symptoms domain and four items in the daily activities domain. A higher score on an item or domain corresponds with worse HRQoL and the raw scores are linearly transformed to a scale ranging from zero to 100. Evidence of validity was identified but no minimum important difference identified.
- VKC symptoms: Reported by the 100 mm VAS assessing photophobia, tearing, itching, and mucous discharge. A decrease in the VAS score from baseline indicated improvement. No validity or minimum important difference were found for the VAS of these symptoms in patients with severe VKC.

## Efficacy

The primary outcome in VEKTIS showed that cyclosporine 0.1% was statistically significantly better than placebo at four months using both treatment regimens, with a between-group difference in the LS mean for cyclosporine 0.1% four times daily treatment versus placebo of 0.76 (95% CI, 0.26 to 1.27; *P* = 0.007) and a between-group difference in the LS mean for cyclosporine 0.1% twice daily treatment versus placebo of 0.67 (95% CI, 0.16 to 1.18; *P* = 0.01).

The average improvement of the four VAS symptoms was larger in the cyclosporine 0.1% four times daily treatment group than in the placebo group (LS mean difference, –19.411 [95% CI, –29.307 to -9.515]) but no statistically significant difference was observed in the cyclosporine 0.1% twice daily treatment group versus the placebo group (LS mean difference, –8.355 [95% CI, –18.402 to 1.693]).

The proportion of responders in the four times daily treatment group was 57.1%, and was 61.1% in the twice daily treatment group as compared with the placebo group, where 34.5% of the patients met the responder definition. A responder was defined as having a mean CFS score during the last three months of treatment that was 50% or less of the baseline value, who was not withdrawn for a reason related to the treatment, did not experience ulceration, and did not use rescue medication.

The results of the symptoms domain section of the QUICK questionnaire showed that the patients in the cyclosporine 0.1% four times daily treatment group consistently achieved a larger magnitude of benefit versus those in the placebo group than the cyclosporine 0.1% twice daily treatment group; where at month four, the four times daily treatment group mean difference versus the placebo group in the symptoms domain was –8.766 (95% CI, –16.403 to –1.129), contrasted with the twice daily treatment group mean difference versus the placebo group in the symptoms domain of –3.817 (95% CI, –11.646 to 4.013).

Patients in the cyclosporine 0.1% four times daily treatment group received at least one rescue medication at a rate of 0.321 (95% CI, 0.203 to 0.460), and patients in the twice daily treatment group received rescue medication at a rate of 0.315 (95% CI, 0.195 to 0.456), compared with the placebo group where patients received at least one rescue medication at a rate of 0.534 (95% CI, 0.399 to 0.667).

Results of outcomes beyond the primary efficacy end point were not adjusted for multiplicity. An important limitation to the external validity of VEKTIS is the clinical interpretation of the primary composite efficacy outcome due to the absence of established validity and a minimum important difference in the primary outcome. Also, clinical interpretation of secondary outcomes must be considered with risk for type I error.

## Harms (Safety)

During the four-month double-blind efficacy phase of VEKTIS, the proportion of patients with at least one adverse event was 42.1% in the cyclosporine 0.1% four times daily treatment group, 33.3% in the cyclosporine 0.1% twice daily treatment group, and 39.7% in the placebo group. Over the full period of the study (including the eight-month safety follow-up phase for a total of 12 months), 58.0%, 54.5%, and 50% of patients experienced at least one adverse event in the cyclosporine 0.1% four times daily treatment group, cyclosporine 0.1% two times daily treatment group, and placebo-cyclosporine 0.1% group (during follow-up, patients in the placebo group were switched to either the four times daily or twice daily cyclosporine 0.1% groups), respectively. There were four different serious adverse events that were determined as not clinically relevant by investigators. During the four-month, double-blind efficacy phase, the placebo group had the highest number of patients withdrawing due to adverse events (four patients [6.9%]). Three patients withdrew due to adverse events (5.3%) in the cyclosporine 0.1% four times daily treatment group, and no patients withdrew due to adverse events in the cyclosporine 0.1% twice daily treatment group. While stinging sensation was not explicitly reported during the double-blind treatment period, “instillation site pain” was reported in six (10.5%) patients in the four times daily treatment group, three (5.6%) patients in the two times daily treatment group, and two (3.4%) patients in the placebo group. No deaths were reported.

## Indirect Treatment Comparisons

No indirect comparisons were identified or submitted by the manufacturer.

## Cost and Cost-Effectiveness

Cyclosporine 0.1% is supplied as 30 single-use containers containing 0.3 mL of unpreserved emulsion at a price of $110. At the recommended dosage of four drops daily to each affected eye, the daily cost is $14.68 per day. According to the clinical expert consulted by CADTH, treatment would be administered in response to VKC symptoms, which may be seasonal or perennial.

The sponsor submitted a cost-utility analysis of cyclosporine 0.1% plus SOC compared with SOC in pediatric patients with severe VKC. SOC was defined as rescue corticosteroid eye drops 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 over a nine-year time horizon (i.e., until patients reached the end of adolescence, defined as 18 years of age). The Markov state transition model had three health states: symptomatic, asymptomatic, and death. In total, 55.4% of patients had perennial VKC and remained in the symptomatic health state; the remaining patients had seasonal VKC and alternated between the symptomatic and asymptomatic health states every six months. Patients in the symptomatic health state accrued treatment-specific utility decrements based on mapping QUICK questionnaire VKC symptoms and daily activities domain scores as reported in the VEKTIS trial. A constant proportion of patients in the symptomatic health state were also assumed to have treatment-emergent glaucoma. Direct medical costs were estimated from Canadian sources with corticosteroid and eye drops use based on the VEKTIS trial.

In the sponsor's base case, cyclosporine 0.1% plus SOC was associated with an 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.

CADTH identified the following key limitations:

- The model structure did not appropriately capture VKC natural history and the relationship between disease severity and costs.
- Relevant comparators that are currently used off-label in patients with severe VKC, such as tacrolimus, were not considered.
- Comparative efficacy was based on the VEKTIS trial, which was noted to have imbalanced treatment and control groups. Efficacy was modelled according to the QUICK questionnaire, though there is a lack of comprehensive evidence regarding its reliability, responsiveness, and validity. In addition, rather than capturing the variance of 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 sponsor's model estimated that the majority (96%) of the benefits of cyclosporine 0.1% plus SOC would occur beyond the clinical trial period (four months).
- The sponsor applied an unvalidated mapping algorithm to estimate utility decrements based on the trial-reported scores on the two QUICK domains. Impact of QUICK domains were separately considered despite being highly correlated, which likely led to overestimation of the impact of treatment on health utilities.
- Although the sponsor claimed to have modelled treatment-emergent impacts of glaucoma and applied disutility values reflective of glaucoma, the probability and cost parameters in the model reflect the incidence and management of elevated intraocular pressure (IOP). Elevated IOP is asymptomatic and often managed with minimal impacts on a patient's quality of life.
- Costs of over-the-counter lubricant eye drops were included, though these costs are not covered by the majority of the Canadian public plans.

The CADTH base-case reanalysis addressed some of the limitations by incorporating monthly efficacy estimates from the VEKTIS trial, removing disutilities associated with the QUICK daily activities domain scores and elevated IOP, and removing the cost of lubricant eye drops. 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 for cyclosporine 0.1% plus SOC to be considered cost-effective at a $50,000 per QALY threshold.

CADTH could not address several key limitations of the submitted model, including uncertainty associated with the model structure and with the clinical efficacy estimates. The comparative clinical benefit of cyclosporine 0.1% compared with off-label treatments remains unknown. Careful consideration is therefore required in interpreting the cost-effectiveness results.

## CDEC Members

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

## October 16, 2019 Meeting

## Regrets

One CDEC member did not attend.

## Conflicts of Interest

None