CADTH

CADTH COMMON DRUG REVIEW

Patient Input

CYCLOSPORINE (Verkazia)

(Santen Inc.)

Indication: Severe vernal keratoconjunctivitis, pediatric (≥4 years)

CADTH received patient input from:

Canadian Organization for Rare Disorders (CORD)

June 12, 2019

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Verkazia (cyclosporine)**
Name of the Patient Group	**Canadian Organization for Rare Disorders**
Author of the Submission	[redacted]
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1. About Your Patient Group

The Canadian Organization for Rare Disorders is registered charity that provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD provides education and resources to patient groups to enable them to better meet their members' needs.

2. Information Gathering

This submission provides a qualitative summary of the feedback received by the Canadian Organization for Rare Disorders (CORD) from several sources: interviews with clinicians (optometrists and paediatric ophthalmologists), and individual semi-structured interviews conducted by CORD.

The purpose of the clinical interviews was to understand the experiences of the patients and families living with vernal keratoconjunctivitis (VKC) and their perceptions about their current therapies as well as the therapy under review, Verkazia. The total patient population affected by vernal keratoconjunctivitis (VKC) is relatively large, but the sub-population that would be indicated for this therapy appears to be very small. In Europe, Verkazia was approved as an orphan drug for a "rare disease." However, unlike many rare diseases, there does not seem to be an active patient support community for this condition, which may be attributable to several unique characteristics. While VKC may have a genetic component and there are families with more than one child affected, it does not present as a familial condition in the usual sense with patterns of inheritance. Moreover, most patients experience only mild or moderate forms of VKC, and even those with severe manifestations will most likely "grow out" of their symptoms beyond adolescence.

Given the ultra-rarity of this condition within a spectrum of a much more populous condition, it was important to get an in-depth understanding of this distinct sub-population from a clinical point of view. How clearly was "severe VKC" differentiated from mild or moderate VKC, or does the "level of severity" remain fairly constant throughout the course of its appearance? Was duration or recurrence of the condition related to severity? As importantly, the clinicians were approached to help identify patients (those with and without Verkazia experience) who may be willing to be interviewed.

We were primarily interested in interviewing those clinicians treating families with children who had been diagnosed with the severe form of VKC as well as the families (parents) themselves. Sadly, it was not easy to locate either Canadian clinicians or patients. The following summarizes our outreach efforts and the characteristics of those interviewed.

We conducted outreach to clinicians and patients through: optometrists (Canadian Optometry Association), pediatric ophthalmologists (Toronto Hospital for Sick Children), and the VKC Facebook support group (global network). We wrote to the clinicians whom we knew or identified through their clinic site and also requested participants through the (closed) VKC Facebook site.

Overall, we conducted one-on-one interviews with ten patient families, which also included an older child in one case.

Given the very small number of participants and the heterogeneity of the population and their experiences, it is not meaningful to present a composite profile of the patient journey; however, where it is feasible and meaningful, this submission summarizes modal responses and central tendencies along with the range of experiences.

One-on-one Interviews were conducted by a single interviewer. The CADTH submission template was used to develop an interview guide; notes were taken during the semi-structured interviews, conducted by a single interviewer. While the questions were structured, they were open-ended and patients were often encouraged to respond in their own words; effort was made to ensure that there was no overt, covert or bias toward any pre-conceived or "desired" answers. Responses were transcribed to a central datasheet, with specific answers grouped by theme.

The following defines the HCPs who participated in the interview:

- 2 optometrists who had treated severed VKC (Ontario and Alberta)
- 2 pediatric ophthalmologists (Ontario and United Kingdom)

All had been in practice for more than 10 years. Both optometrists practiced as part of a clinical group and were members of the Canadian Optometry Association. They indicated they had encountered several cases of moderate-to-severed VKC in their practice; however, one clinician did not have an active diagnosed severe case at this time, while the other did.

Both ophthalmologists practiced in a children's hospital setting within a department of ophthalmology or an Eye Centre, where they were part of an ophthalmology team, doing research as well as providing clinical care. They reported that they had treated many cases throughout their careers and were actively treating several children (including adolescents) at this time.

The following describes the patients (parents) interviewed:

- 3 parents of children with moderate to severe VKC without Verkazia experience (Ontario)
- 3 parents (plus one child) with severe VKC with Verkazia experience (Ontario)
- 4 parents of children with severe VKC with Verkazia experience (UK)

Interviews were conducted by phone, SKYPE, or WHATsApp.

The following describe the characteristics of the children with severe VKC discussed in the interviews.

- 3 children with moderate to severe VKC (no Verkazia experience), all boys, range of ages from 5 to 15 years; diagnosed for five months to five years; one of the families lived in a rural community and two families lived within metropolitan area with a major children's hospital; all were being treated locally by the optometrist; however one was in the process of referral to the pediatric ophthalmologist
- 3 children with severe VKC (with Verkazia), all boys, range in ages from 8 to 16 years; diagnosed for three to 6 years; treated by pediatric ophthalmologists
- 4 children with severe VKC (three with Verkazia experience); three boys and one girl, ages 6 to 14 years old, treated at eye clinics in UK. One patient was diagnosed with atopic keratoconjunctivitis as well as VKC. Two of the children were in one family.

3. Disease Experience

Regardless of where the patient lived, they described similar journeys to diagnosis and treatment. Six out of the ten families said it had been somewhat or very difficult to get to the "right" diagnosis. In Canada,

children were initially seen by their family doctor, pediatrician, or optometrist. In three cases, parents reported one or more visits to the ER (where the child was examined and dismissed with a prescription) before being referred to an ophthalmologist.

"It was frightening because the doctor kept saying it was nothing serious; lots of children have allergies that could be managed with regular treatment, but we just didn't feel right."

"I don't know if it would have made any difference if we had gotten to a specialist earlier, but it might have saved us some much anxiety and wasted time not knowing what was wrong."

"We were relieved just to get a diagnosis of VKC even though we were really frightened when we learned there was no real treatment and that he could develop glaucoma or cataracts; he might even lose his sight. We were like … but he is just 8 years old. How can there be nothing we do to prevent this?"

About two-thirds (seven out of ten) of the parents reported their children had experienced frequent episodes of hay fever, asthma and/or other allergic reactions. Parents of all of the children reported noticing symptoms that included red eyes, puffiness, and a watery fluid or mucous discharge that would often develop into a "crust" overnight. All of the parents said their children complained of itching or irritation (some foreign substance) in the eyes (under the lids). Parents also noticed what they described as "bumps" on the upper and/or lower eyelids and on the cornea. The children complained of "blurry" vision; they had a tendency to close their eyes, especially in the daytime.

In almost all cases, these symptoms were seasonal, first appearing in the spring and generally lasting for about five to eight months. However, in three cases, the parents reported that the symptoms were present for longer periods and (sometimes) throughout year.

Symptoms interfered 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 impact on the ability to take part in many social and recreational activities.

"Looking back, it started when he was only two or three, with red eyes and regular discharge. We were told it was allergies and, in the beginning, it would clear up with eye drops (allergy medication) but the symptoms kept coming back. But when he almost fell down a flight of stairs because his eyes were so swollen that he couldn't see, we knew we needed to do something else."

"It was spring, and he had just turned seven. The school said it looked like "pink eye" and he had to be kept at home so he wouldn't infect the other children. But it got a whole lot worse; his eyes were almost swollen shut and he complained they felt like there was "stuff" in them. We took him to ER where they diagnosed conjunctivitis and prescribed more eye drops in addition to the ones he was already taking. Two weeks later, we were back in the ER and that's when we were referred to the eye clinic. That's where we learned he had VKC. We ended up with prescriptions for eight medications."

"Both of our boys have VKC but only one is severe; the other is mild. We were told he would likely outgrow it, but It's been four years and [redacted] still can't even go out in the sunlight because his eyes hurt too much. We are doing eye drops four times a day, but they only helped a little. We still ended up going to the hospital about once month."

"I feel like [redacted] missed out on all of the normal things kids do. He couldn't join any sports teams, couldn't go to summer camp like his brother. He had a hard time reading and playing video games was tough."

"Before all this …. he was just the happiest toddler, always running around and laughing. I know he is self-conscious about how he looks, and he will withdraw, even with strangers. Luckily, he has a couple of really close friends who he has known for years."

"The medication is pretty disruptive. When you have to do eye drops, some of them every two hours and others three or four times a day, it means someone has to be constantly available. Even when my son was older, it wasn't possible to rely on him to keep track of all the different medications and their schedules. The worst was travelling, which was a nightmare."

"You never feel like you can just relax and let your guard down. The medication has to be given several times a day and when you stopped, the symptoms would come back, sometimes worse than before."

"We don't know any other families with this condition, so we have felt pretty much alone in learning how to deal with this. It's been six years and we finally feel like his eyes are getting better. Maybe he is finally outgrowing this."

4. Experiences With Currently Available Treatments

Until recently, there has been no approved treatment specific to vernal keratoconjunctivitis, but there are treatment guidelines using "off label" treatments, the sequencing of which are based on severity of the condition and successive failures at earlier stage therapies. Most of the parents interviewed whose children have been diagnosed for several years reported experience with almost all of the available therapies (antihistamines, lubricants, mast cell stabilizers, steroids, immunosuppressants). Even parents whose children were more recently diagnosed had gone through several treatment regimens, usually taking some drugs sequentially and others concomitantly.

All parents reported they had been prescribed antihistamines when the children first developed symptoms. Some were prescribed three or four different types and formulations. Half of the ten parents (including those whose children had "moderate-to-severe" disease) said they felt the antihistamines had worked in the beginning to reduce or even stop symptoms. The children's' eyes cleared and dried up, the itching and pressure were much better, and the children were able to go outdoors without discomfort. The other five parents felt that the initial eye drops had never provided relief or addressed the symptoms. There was no apparent correlation between the age of initial treatment and effectiveness of antihistamines.

None of the patients reported their children were "symptom-free", that is, no red eyes, swollen lids, mucous weeping and/or ability to tolerate sunlight, while on antihistamines with or without another drug (mast cell stabilizer) in combination. (Parenthetically, one parent who also had a son with mild VKC, reported they were able to reduce and even prevent symptoms for this child with antihistamines.)

Eight of the patients had in the past or were currently using steroids. The only patients who had no steroid experience were one "moderate-to-severe" patient and one patient whose parents had rejected steroids as an option and requested access to tacrolimus (UK family). Six out of eight patients reported that the steroids were reasonably effective, especially if used on a continuous basis as a prophylactic (preventive) therapy before the child developed symptoms. Almost all parents expressed concerns about long-term steroid use, although there were different perceptions around the "trade-off" between short-term symptom management and long-term potential adverse effects. Another concern with steroids was the frequent dosing and constant monitoring (return to the clinic) to get the dosage right.

Eight of the patients had experience with cyclosporine A eye drops and one with tacrolimus eye drops. Not all of the parents were aware of the strength of the formulation but four reported starting with Restasis (0.05%) while the others were unsure. Six of the parents indicated that the clinician had indicated s/he was increasing the strength and they received the eye drops from the pharmacy (that prepared the drug). One parent said she was told the strength had been increased to 2%. Five out of eight parents were mostly satisfied with the effects of cyclosporine A in managing symptoms, as was the parent using tacrolimus. None said the red eyes or puffiness were totally gone but the children were able to take part in social activities and to be outdoors. Three of the parents indicated they were "very worried" about increasing the strength of the cyclosporine, though none reported any adverse effects (other than initial stinging or irritation that dissipated). The drops were, for the most part, well tolerated although they did have to be administered three to four times a day.

All of the patients said with cyclosporine, they had been able to reduce or completely eliminate the use of steroids, which, for some parents, was *"a big relief"* even though cyclosporine was not risk-free.

When asked how they decided which medication to choose, six out of ten said they relied on their physician's recommendation. Only two said they also searched other options on line; the others said they also weighed the experience of parents in their support group, even bringing a request to the physician. Overall, the response to available treatments (not including Verkazia) varied; however, none of the patients with severe VKC reporting complete remission of symptoms with any single medication or combination.

"We had tried several brands of allergy medicines before we found one that seemed to work, at least for several months. But then it either stopped working or maybe [redacted] condition just got worst."

All parents said they were eventually prescribed two or more medications to be used in combination.

"It was a challenge to come back every two weeks to have a review of the medicines."

"We were concerned about taking so many drugs, especially since they all had potential long-term effects. We really didn't like the idea of steroids but nothing else was working. The doctor suggested we at least try them to see if how he responded. We agreed on a low dosage but then had to keep increasing."

"My doctor said I didn't need to worry about [our son] taking steroids since it would be only for a short time and anyway, we were not injecting it like for arthritis but only using on the outside. But I was still worried. On the other hand, I wasn't thrilled to switch to cyclosporine since I knew it was an immunosuppressant and also could have long-term effects."

"For a while, we were taking about eight drugs all together, including an allergy drug, steroid, and then cyclosporine (Restasis) plus a dry-eye lubricant and aspirin. It might have been easier if they were all on the same schedule but not at all. Luckily, [our son] didn't seem to have much by way of side effects."

"When we lived in Italy, our daughter had been taking tacrolimus, but the physician didn't want to prescribe it here, so we had to switch to cyclosporine. Unfortunately, the standard dosage didn't have much effect, so we were prescribed a special compound, which was not available at our eye clinic. It was also not covered by our drug plan, so we had to pay for it out-of-pocket. So long as it worked, we felt it was a better choice than steroid."

5. Improved Outcomes

Parents were universal in wanting a treatment that reduces any potential long-term harm to their child's eyes as well as manages the symptoms on a reliable day-to-day basis. Parents had been informed that the condition will get better and likely be resolved as the child got older, but they are not confident nor were they reassured that damage sustained when the child was young might not have a permanent impact. Few parents had a history of VKC in the family; they also were not acquainted with other families with the same condition (except the occasional meeting in clinic) so it is understandable that they felt lost and uncertain about the treatment choices. Moreover, some said they had been prescribed many different medicines, often without fully understanding how each worked to treat the condition or what they could expect.

"Sometimes I think the doctor is just doing "trial and error" with our son; she prescribes a new drug every time we come in and doesn't really let us know how it works or what we can expect. When we ask how we know whether [this new drug] is working, she usually says, 'you'll know in about two weeks.' That's not much information."

Since all parents had experience with steroids and/or immunosuppressants, they expressed their needs relative to these; specifically, they called for interventions that were:

- Immediately effective in reducing symptoms
- Preventive (used as prophylactic treatment) before child has symptoms or on a regular schedule to prevent symptoms
- Carried little or no risk for long-term negative effects
- Required less frequent administration
- Replaced rather than added to other treatments
- Was fully covered by their drug plan

6. Improved Outcomes

The patients in Ontario who had access to Verkazia (CsA CE) were being treated as part of an "extended trial", primarily through the hospital. All had been on Verkazia therapy for only six weeks or less, so the

experience was limited. Prior to Verkazia, all of the children had been using a formulation of cyclosporine A (at higher than the 0.05% concentration for Restasis). One parent did report that she noticed an immediate improvement; her son's eyes were less watery; he could see better, and he felt there was "less pressure" on the eye. The other two patients likewise said they were hopeful that Verkazia would be more effective in keeping symptoms to a minimum and allow their children more freedom. They found it easier to use (once daily).

Parents reported that the children had experienced few or no side effects to the drug. The most frequent complaint was pain or tingling while the drug was being administered.

In the UK, the parents received medications as part of their healthcare through their local trust and the eye centre. All those with three to 12 months experience said they were very pleased with the switch to Verkazia. One parent reported she was able to reduce her clinic visits to every other month, which was a huge savings in time since the clinic was not nearby. Another mom reported there had been no more visits to the ER since starting Verkazia, whereas she had been at least twice in the past year. "We were able to reduce and to keep his symptoms from recurring."

"We had been told that [his] symptoms would subside over time and that there was no apparent permanent damage to the eyes, but we are much more hopeful now. I can't help but believe that having few symptoms or less severe problems will contribute to a long-term full recovery."

"We find that it is easier to travel with Verkazia. There are fewer vials and we only have to use it once a day, at night. It may not sound like much, but it makes a big difference, especially when you have other kids and also two jobs.

7. Anything Else?

It is curious that there is no patient support community for this community, given the challenges in managing symptoms and choosing the best therapies. When Canadian parents were asked about value of a parent support group, they indicated they would like to be able to speak to others who had gone through the same experience. They especially wanted to know what they could anticipate as their children get older. Does the condition get worse? When do symptoms subside? Should they be concerned about the long-term effects of steroids? What about immunosuppressants for young children? Could there be a *permanent* impact on their immune systems?

The parents in Canada that we interviewed had not been aware of Verkazia prior to the recommendation from their physician or learning about it through this interview. Because VKC and especially severe VKC is a rare condition, support groups around for those with limited or no sight (National Institute for the Blind; Foundation Fighting Blindness) did not know about this condition, nor were they prepared to do outreach (lack of resources).

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No, this was completed by CORD without additional outset help.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No, information was collected, analyzed, and prepared for submission by CORD.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None				

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

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Position: President & CEO
Patient Group: Canadian Organization for Rare Disorders
Date: 23 June 2019