CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

CYSTEAMINE OPHTHALMIC SOLUTION (CYSTADROPS — Recordati Rare Diseases Canada Inc.)
Indication: Treatment of corneal cystine crystal deposits (CCCDs) in adults and children from 2 years of age with cystinosis.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that cysteamine hydrochloride (CH) 0.55% ophthalmic solution be reimbursed for the treatment of CCCDs in adults and children from two years of age with cystinosis only if the following conditions are met:

Conditions for Reimbursement

Initiation Criteria
1. Patient has a diagnosis of cystinosis and evidence of CCCDs.

Prescribing Condition
1. Patient must be under the care of an ophthalmologist experienced in the management of the ocular manifestations of cystinosis.

Pricing Condition
1. Reduction in price.

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Reasons for the Recommendation

1. In one open-label, phase III randomized controlled trial (RCT; the Cysteamine Hydrochloride for nephrOpathic Cystinosis [CHOC] study, N = 32), CH 0.55% ophthalmic solution resulted in a statistically greater decrease in CCCDs, as measured by the change from baseline in the in vivo confocal microscopy (IVCM) total score, compared with CH 0.10%. The comparative benefit of CH 0.55% versus CH 0.10% was supported by greater improvements in corneal cystine crystal score, crystal layer thickness by optical coherence tomography, and patient- and investigator-assessed photophobia in the CH 0.55% treatment group.

2. Based on a CADTH reanalysis of the manufacturer-submitted economic model, CH 0.55% drops were associated with an incremental cost-utility ratio (ICUR) of $736,828 per quality-adjusted life-year (QALY) gained compared with best supportive care (BSC). However, this estimate is associated with significant uncertainty due to limitations in the submitted model structure, comparative efficacy information, and strong reliance on assumptions. Based on the CADTH reanalysis, price reductions of more than 80% and 87% would be required to achieve ICURs below $100,000 and $50,000 per QALY, respectively.

3. Cystinosis is a rare hereditary disease with a prevalence of approximately 1 in 100,000 to 1 in 200,000 births and is associated with a high rate of ocular complications. As there are no other commercially available standardized treatments approved for the ocular complications of cystinosis in Canada (only compounded cysteamine ophthalmic drops available from specialty pharmacies) CH 0.55% addresses an unmet need for treatments for this condition.

Discussion Points

- The committee noted that oral cysteamine, which is indicated for the treatment of nephropathic cystinosis, does not reach the avascular cornea. The committee discussed that patients with ocular manifestations of cystinosis are currently treated with cysteamine ophthalmic drops compounded by specialty pharmacies. However, clinical expert input indicated that there is a lack of standardization with respect to the methods and formulation for the compounded drops. The compounded drops' short shelf-life, need for continuous refrigeration, and recommended frequency of administration (every one to two hours) are potentially burdensome for patients and likely to lead to difficulties with adherence. The committee considered the recommended frequency of administration for Cystadrops (up to four times daily), and the fact that opened bottles require no refrigeration as less likely to be burdensome for patients. However, clinical trial evidence that the reduced frequency of administration results in improved adherence is lacking.

- The committee considered that, with the granting of a Notice of Compliance to Cystadrops by Health Canada, compounded cysteamine ophthalmic drops that are currently in use may no longer be available.

Background

Cystadrops (cysteamine ophthalmic solution) has a Health Canada indication for the treatment of CCCDs in adults and children from two years of age with cystinosis. It is available as a viscous topical ophthalmic solution containing CH 0.55% (3.8 mg/mL cysteamine). The Health Canada–approved dosage is one drop in each eye, four times a day during waking hours. The dose could be decreased progressively (to a minimum total daily dose of one drop in each eye) depending on the results of ophthalmic examinations (such as CCCDs, photophobia).

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by the CADTH Common Drug Review: a systematic review of RCTs of Cystadrops and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from three clinical experts with experience in treating patients with cystinosis.

Summary of Patient Input

No patient group input was received for this submission. However, information from one patient group input submission from the Canadian Organization for Rare Disorders for the CADTH review of Procysbi, a systemic therapy for the treatment of nephropathic cystinosis, was considered. Information for the submission was gathered from testimonials, individual semi-structured interviews, and a survey. Relevant input from the submission included:

- Those living with cystinosis experience gastrointestinal symptoms (vomiting, diarrhea, and abdominal pain), muscle wasting, swallowing difficulties and gagging, halitosis, foul body odour, crystal buildup in the cornea leading to corneal disease and photosensitivity, extreme thirst and urination, reduced cognitive abilities, and rickets and softening of bones. Other impacts of the disease include kidney failure, multiple organ failure, and diabetes.
- Cystinosis has significant impact on patients and their caregivers, including interruption of sleep to administer immediate-release cysteamine, multiple visits to physicians and other health care professionals, stress associated with financial burden related to the cost of treatment and supportive care, and social isolation.
- Crystal buildup in the cornea and/or photosensitivity was the most commonly reported symptom in the survey.

Clinical Trials

The systematic review included one open-label, parallel-group RCT comparing Cystadrops (CH, 0.55%) with a CH 0.10% ophthalmic solution in patients with cystinosis and CCCDs. The CHOC study (N = 32; conducted in 2013 at two centres in France) randomized patients (1:1) to CH 0.55% or CH 0.10%. Patients received the study treatment for 90 days, and were assessed at day 30 and day 90. In both treatment groups, patients were to administer one drop of the study medication in each eye four times daily at approximately 8:00 a.m., 12:00 p.m., 4:00 p.m., and 8:00 p.m. Patients and investigators were not blinded to treatment assignment.

Patients in the CHOC study were older than two years of age, had a diagnosis of nephropathic cystinosis, and had CCCDs demonstrated by slit-lamp examination. One patient in the CH 0.10% group was lost to follow-up and excluded from the analysis. Eleven patients in each group underwent the IVCM procedure at baseline and could therefore be evaluated for the primary end point, IVCM total score.

There were several of limitations associated with the CHOC study. Cystadrops is indicated for the treatment of CCCDs and is expected to provide clinical benefit in improvement in cystinosis-related ocular symptoms through a reduction in these deposits. There was limited evidence found for an association between the measures of corneal cystine crystal burden, including the primary end point, and patient-important outcomes. There was no evidence found for the validity of the patient- and investigator-rated photophobia scales and how they relate to patients' abilities to function or quality of life. Minimal clinically important differences were not found for the efficacy outcomes. The lack of blinding of patients and investigators to treatment assignment also meant there was a risk of bias in the efficacy outcomes, particularly in photophobia due to the subjective nature of the scales used. Finally, the comparator in the CHOC study was of a concentration of CH and dosage regimen (0.10% instilled four times per day) considered by the clinical experts consulted for this review to be less effective than the treatment regimen typically used in Canada (pharmacy-

compounded CH 0.55% instilled every one to two hours during the waking day). The CHOC study does not provide any efficacy data on Cystadrops compared with CH ophthalmic drops compounded by pharmacies, or BSC without topical CH treatment.

Given that patients with cystinosis are expected to require treatment for corneal cystine crystal buildup throughout their lives, a 90-day treatment period does not provide sufficient evidence for the long-term efficacy and safety of CH 0.55% ophthalmic drops.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed the following:

- IVCM total score: IVCM is a microscopy technique able to directly visualize corneal cystine crystals. Investigators acquired and selected five to 10 IVCM images with a field of view of 0.4 mm x 0.4 mm from each of seven corneal layers in the central cornea for rating. A reader blinded to treatment assignment rated images using an ordinal scale ranging from 0 to 4 (0 equals no crystals; 1 equals fewer than 25% of deposits; 2 equals 25% to 50% of deposits; 3 equals 50% to 75% of deposits; 4 equals 75% to 100% of deposits) and a total score was obtained by summing up the individual layer scores. IVCM total score has a range of 0 to 28, with higher scores indicating greater crystal density and/or burden.
- Cystinosis corneal crystal score (CCCS): CCCS is a method for assessing corneal cystine crystal density by slit-lamp examination. Scoring is on a scale of 0 to 3 with 0.25 increments, based on a library of reference slit-lamp photographs. A higher score indicates greater corneal crystal density.
- Corneal crystal layer thickness by optical coherence tomography (OCT): The thickness of the corneal crystal layer was measured on OCT images of the central cornea.
- Patient-rated photophobia: Photophobia was rated by the patient on an ordinal scale from 0 (no photophobia, no discomfort [none]) to 5 (extreme difficulty with light requiring the patient to remain inside, cannot bear natural light even with sunglasses [extreme]), with higher values corresponding to more severe photophobia.
- Investigator-rated photophobia: Photophobia was rated by the investigator on an ordinal scale from 0 (no photophobia) to 5 (unable to open eyes eve indoors [extreme]), with higher values corresponding to more severe photophobia.
- Local adverse drug reactions (LADRs) upon instillation: The occurrence of local symptoms (redness, blurring, itching, stinging, and burning) were recorded following each instillation of the study medication, along with time of instillation, whether local symptoms lasted for less than or longer than one hour, and the severity of each local symptom on an ordinal scale from 1 (mild) to 4 (unbearable).

The primary outcome in the CHOC study was change in corneal cystine crystal density, as assessed using IVCM total score, from baseline to day 90. IVCM total score was assessed in 22 eyes in the CH 0.55% group and 20 eyes in the CH 0.10% group. There were no outcomes available for health-related quality of life.

Efficacy

- The primary end point of the CHOC study, change in IVCM total score from baseline to day 90, showed a statistically significantly greater improvement with CH 0.55% versus CH 0.10% (mean difference of –3.84 [95% confidence interval, –5.58 to –2.11]). A minimal clinically important difference for IVCM total score was not found and the clinical significance of this result is unknown.
- Mean CCCS decreased (improved) from baseline to day 90 in the CH 0.55% group and not in the CH 0.10% group (mean change of –0.592 [standard deviation or SD of 0.523] versus 0.105 [SD of 0.240]).
- Mean corneal crystal layer thickness by OCT decreased from baseline to day 90 in the CH 0.55% group and not in the CH 0.10% group (mean change of –46.3 µm [SD of 55.3 µm] versus 10.6 µm [SD of 43.6 µm]).
- Mean investigator-rated photophobia decreased (improved) in the CH 0.55% group (mean change of –0.633 [SD of 0.765]) and not in the CH 0.10% group (mean change of 0.065 [SD of 0.442]).
- Mean patient-rated photophobia decreased (improved) by a numerically greater amount in the CH 0.55% group (mean change of –0.267 [SD of 0.583]) and not in the CH 0.10% group (mean change of 0.226 [SD of 0.717]).

Statistical interpretation of efficacy results beyond the primary end point was limited by the lack of control for multiplicity and potential for inflated type I error. There were no statistical analyses available for outcomes pertaining to vision-related function or complications of CCCDs.

Harms (Safety)

In the CHOC study, adverse events (AE) classified as eye disorders were more common with CH 0.10% (68.8% of patients) than with CH 0.55% (33.3% of patients). There was one ocular serious AE, corneal graft rejection, in a patient receiving CH 0.10% who had recent corneal transplant surgery. There was one withdrawal due to AE in the CH 0.55% group due to allergic conjunctivitis.

LADRs upon instillation (stinging, redness, burning, blurred vision, and itching) lasting less than an hour were reported in all patients in the CHOC study receiving CH 0.55% and 68.8% of patients receiving CH 0.10%. Higher percentages of patients in the CH 0.55% group versus the CH 0.10% group reported LADRs of each severity and of each type. For LADRs lasting more than an hour, at least one LADR was reported in 33.3% of the CH 0.55% group and 50.0% of the CH 0.10% group.

A long-term, single-arm trial, the OCT-1 study, was conducted in eight patients treated with CH 0.55%. The trial was not included in the systematic review due to the lack of a comparator group. The results of OCT-1 suggested that LADRs decreased in frequency and/or were perceived by patients to improve over 24 months of treatment.

Cost and Cost-Effectiveness

CH 0.55% is available in 5 mL vials containing 3.8 mg/mL of cysteamine, which must be replaced every seven days. At a price of $1,986 per vial, the annual cost per patient is $103,272.

The manufacturer submitted a cost-utility analysis comparing CH 0.55% (four drops in each eye every day) with BSC, which was described as symptomatic treatment and supportive care for ophthalmic events (e.g., ophthalmologist visits and procedural costs), in patients two years of age or older with CCCDs due to cystinosis. The model was conducted from the Canadian public health care payer perspective over a lifetime time horizon (average 25 years). The manufacturer submitted a cohort-level Markov model, with two health states: “alive” and “dead.” The model focused on the ocular components of cystinosis and did not consider the non-ocular components of cystinosis. While in the alive health state, patients could experience ophthalmic events that represented disease worsening, such as photophobia, visual impairment, band keratopathies, blepharospasm, filamentary keratitis, and corneal vascularization. Patients could experience one or more of these events during each three-month cycle. Event probabilities for patients receiving CH 0.55% were derived from the results of the CHOC study, while a mix of natural history data and clinical expert input was used to inform BSC. All patients entered the model in the alive state in near perfect health; costs and disutilities were applied for each ophthalmic event based on either published literature or consultation with a clinical expert for utilities, and clinical experts for resource use and costing from resource use, and costing from the Ontario Ministry of Health and Long-Term Care Schedule of Benefits. In the manufacturer’s base case, CH 0.55% was associated with an incremental cost per QALY gained of $162,755 versus BSC.

CADTH identified the following key limitations with the manufacturer’s submitted economic analysis:

- The model consisted of two health states (alive and dead), which does not allow adequate consideration of clinically meaningful changes that patients with cystinosis experience. Considering only an alive and dead state may be appropriate if a treatment is shown to impact mortality, which CH 0.55% does not. The manufacturer‘s model considered only ocular components without factoring in quality-of-life impacts with regards to the other components of cystinosis.

- CADTH noted that compounded cysteamine ophthalmic drops may be currently used in Canada, but given Health Canada guidelines stating compounded therapies should no longer be used should a product like Cystadrops become available, this was not deemed to be a relevant comparator.

- The manufacturer’s trials do not compare CH 0.55% with BSC, and no indirect comparison was presented. Thus, the comparative benefit of CH 0.55% relative to BSC remains uncertain.

- The CADTH clinical review identified limitations with the clinical studies (open-label nature of the trials, validity of the outcome measures, control groups, lack of long-term data) that introduced increased uncertainty with the efficacy of CH 0.55%.
- The utility and disutility values used were based on assumptions, and considered uncertain. The baseline utility value and the disutility values for photophobia appear to overestimate the benefit of CH 0.55%.
- Several clinical input assumptions, including those related to compliance, age at treatment initiation, and the likelihood and duration of band keratopathies, were not representative of clinical practice, according to feedback from the clinical experts consulted by CADTH. This increased the uncertainty in the results of the economic evaluation.

CADTH undertook reanalyses considering a baseline utility value deemed more representative of the current Canadian population; alternate disutility values for photophobia and blindness; age at model entry based on trial data (17 years of age); a lower compliance rate; removal of incidence of band keratopathy; and updated vision loss costs to reflect the payer perspective. The revisions resulted in CH 0.55% drops being associated with incremental costs of $1.7 million and incremental QALYs of 2.34, which produced CADTH's base case ICUR of $736,828 per QALY gained for CH 0.55% versus BSC. A price reduction of more than 80% and 87% was required to achieve an ICUR below $100,000 and $50,000 per QALY, respectively. The results are highly uncertain given the limitations with the model structure and the comparative effectiveness that could not be addressed.

CDEC Members

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

May 15, 2019 Meeting

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None