CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

CYSTEAMINE DELAYED-RELEASE (PROCYSBI — HORIZON PHARMA IRELAND LTD.)
Indication: Nephropathic cystinosis

RECOMMENDATION:
The Canadian Drug Expert Committee (CDEC) recommends that delayed-release cysteamine be reimbursed for treatment of nephropathic cystinosis, if the following criterion and conditions are met:

Criterion:
For use in patients with an established diagnosis of infantile nephropathic cystinosis with documented cystinosin, lysosomal cystine transporter gene mutation.

Conditions:
- The patient is under the care of a physician with experience in the diagnosis and management of cystinosis.
- Significant reduction in price.

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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.

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For use in patients with an established diagnosis of infantile nephropathic cystinosis with documented cystinosin, lysosomal cystine transporter gene mutation.

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Reasons for the Recommendation:

1. Nephropathic cystinosis is a life-threatening genetic disease with a prevalence of approximately 1 in 100,000 to 1 in 200,000 births. As there are no other treatments approved for nephropathic cystinosis in Canada, delayed-release cysteamine addresses an unmet need for treatments for this condition.
2. Immediate-release cysteamine (Cystagon), which is no longer available in Canada, was regarded as the standard of care for nephropathic cystinosis in Canada. In one 8-week, open-label, randomized, crossover, noninferiority trial (RP103-03; N = 43), reductions in white blood cell (WBC) cystine levels during treatment with delayed-release cysteamine were similar to levels observed during treatment with immediate-release cysteamine. In the intention-to-treat (ITT) population, least squares mean values for immediate-release cysteamine and delayed-release cysteamine were 0.74 and 0.53 nmol half-cystine/mg protein, respectively, with a difference of –0.21 (standard error 0.13) nmol half-cystine/mg protein. The upper limit of the 95.8% confidence interval (CI) was lower than the noninferiority margin of 0.3 nmol half-cystine/mg protein in the per-protocol and the ITT analyses, suggesting noninferiority of delayed-release cysteamine to immediate-release cysteamine for WBC cystine levels.
3. Limited data are available to inform an understanding of the cost-effectiveness of delayed-release cysteamine compared with supportive treatment alone. CADTH Common Drug Review (CDR) re-analysis of a manufacturer-submitted model, which used baseline disease parameters extracted from a historical cohort study and assumed that the treatment effects of delayed-release cysteamine were similar to those of immediate-release cysteamine, concluded that delayed-release cysteamine was not cost-effective compared with no treatment. Even with a price reduction of 95%, the estimated incremental cost per quality-adjusted life-year (QALY) for delayed-release cysteamine in the analysis was more than $100,000. At the submitted price ($11.30 per 25 mg capsule, $33.89 per 75 mg capsule), the annual cost of treatment per patient is expected to range from $136,000 (body surface area of 0.63 m^2) to $321,000 (body surface area of 1.50 m^2).

Discussion Points:

- CDEC discussed the potential for delayed-release cysteamine to meet an unmet need for treatment of nephropathic cystinosis. CDEC recognized that immediate-release cysteamine had never been approved for use in Canada and was available only through Health Canada's Special Access Program. Since immediate-release cysteamine became unavailable in Canada after the approval by Health Canada of delayed-release cysteamine, there are no other existing treatment options for patients with nephropathic cystinosis, which is a life-threatening condition.
- CDEC discussed that delayed-release cysteamine was associated with significant gastrointestinal adverse effects, although the relative contribution of the medication and the underlying disease was not clear. Patients who received delayed-release

cysteamine had lower use of proton pump inhibitors than those who received immediate-release cysteamine during study RP103-03. The Canadian product monograph for delayed-release cysteamine cautions against concomitant use of proton pump inhibitors or other drugs that increase gastric pH because of variations in cysteamine absorption with delayed-release cysteamine. Therefore, one of the manufacturer-proposed benefits with delayed-release cysteamine as compared with immediate-release cysteamine (i.e., reduced adverse effects including gastrointestinal adverse effects) was not supported by data from the reviewed pivotal study.

Background:

Delayed-released cysteamine has a Health Canada indication for the treatment of nephropathic cystinosis. Delayed-release cysteamine reduces the accumulation of lysosomal cystine. It is available as 25 mg and 75 mg oral capsules and the Health Canada–approved maintenance dose for cysteamine-naive patients is 1.30 g/m^2 per day, divided into two equal doses given every 12 hours.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials of delayed-release cysteamine and a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience treating patients with nephropathic cystinosis, and information submitted by a patient group about outcomes and issues important to patients and caregivers who are affected by nephropathic cystinosis.

Patient Input Information

The Canadian Organization for Rare Disorders (CORD) was the only group to respond to the call for patient input. Information for the CORD submission was gathered from testimonials, individual semi-structured interviews, and a survey. The following is a summary of key input from the perspective of the patient group:

- 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 families, including interruption of sleep to administer immediate-release cysteamine, multiple visits to physicians and other health care professionals, and financial stresses related to the cost of treatment and supportive care. Caregiver stress is common, especially for those caring for young children with cystinosis and this is related to the burden of medication administration, regular gastrointestinal symptoms, and social isolation of the caregiver and patient.
- There is also a substantial financial burden on families, including the direct costs for medications, supplements and other supplies, the non-reimbursed costs of health care visits, household expenses for modifications or other repairs, and the loss of income when a parent has to reduce work hours or quit job to provide continuous home care for their a child.

Clinical Trials

The CDR systematic review included one randomized, crossover, open-label, noninferiority trial in patients with nephropathic cystinosis (study RP103-03; N = 43). The study was designed to test noninferiority of delayed-release cysteamine (Procysbi) and immediate-release cysteamine (Cystagon). Patients were greater than and equal to 6 years old, had nephropathic cystinosis and were on a stable dose of immediate-release cysteamine sufficient to maintain their WBC cystine level at less than and equal to 2.0 nmol half-cystine/mg protein. There were two treatment periods of three weeks each, with no washout period between treatments. The primary outcome of the study was mean peak WBC cystine levels. Noninferiority testing of delayed-release cysteamine compared with immediate-release cysteamine was based on WBC cystine levels. No trials were available comparing delayed-release cysteamine to placebo or any other treatments.

The key limitations of Study RP103-03 were: the small sample size, short duration, noninferiority design, and surrogate primary outcome (WBC cysteine levels).

Outcomes

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

- Health-related quality of life was measured by the PedsQL 4.0 Generic Core Scale, which is comprised of 23 items organized under the categories of physical functioning, emotional functioning, social functioning, and school functioning. The scores are transformed into a 0 to 100 scale, with higher scores indicative of a higher health-related quality of life. The minimal clinically important difference (MCID) has not been determined.
- WBC cystine levels were used to assess the primary outcome for study RP103-03. Newly diagnosed nephropathic cystinosis patients are found to have WBC cystine levels in the range of 3 to 10 nmol half-cystine/mg of protein, while control individuals and heterozygous carriers generally have levels between 0.2 and 0.5 nmol half-cystine/mg of protein, respectively. While on cystine-depleting treatment, targeted levels are usually below 1 nmol half-cystine/mg of protein. The WBC cystine level at which progressive renal failure and extra-renal complications can be prevented is unknown. The minimal clinically important reduction in WBC cystine in patients with nephropathic cystinosis has not been established.
- Adherence to therapy was assessed by counting missed study drug doses during the trial and this was based on patient self-report or medication counts performed during clinic visits.
- Swallowing difficulties were measured using a 10-point visual analogue scale (VAS), with 2-point increments in scoring from 0 (no pain) to 10 (very much pain). The MCID is not known for this scale.
- Incidence of serious adverse events (SAEs) and adverse events, including gastrointestinal and non-gastrointestinal adverse events.

Outcomes identified by patient groups as important included: survival, quality of life, patient growth, kidney function, and adherence to therapy.

Efficacy

- There was no statistical testing performed on the health-related quality of life data and there did not appear to be any differences between delayed-release cysteamine and immediate-release cysteamine in study RP103-03.
- No patients died during the study.
- In the per-protocol population, the least squares means for WBC cystine at week 3 for delayed-release cysteamine and immediate-release cysteamine were 0.52 and 0.44 nmol half-cystine/mg protein, respectively (mean difference: 0.08; 95.8% CI, 0.012 to 0.15; $P < 0.001$). In the ITT population, the least squares means for WBC cystine at week 3 for delayed-release cysteamine and immediate-release cysteamine were 0.53 and 0.74 nmol half-cystine/mg protein, respectively (mean difference: –0.21; 95.8% CI, –0.48 to 0.06; *P* value not reported). The upper limit of the 95.8% CI was lower than the noninferiority margin of 0.3 nmol half-cystine/mg of protein in the per-protocol and the ITT analyses.
- There were two patients (5%) with renal impairment and one patient (2%) with renal failure during treatment with delayed-release cysteamine, classified as mild renal failure. There was one patient (2%) with renal impairment during treatment with immediate-release cysteamine.
- Eight patients were reported to have missed study doses during the trial, including five patients while taking delayed-release cysteamine and three patients while taking immediate-release cysteamine.
- Eight of 39 patients (21%) reported a swallowing VAS score of greater than 4 at one time point during the study; 3/39 patients (8%) reported VAS scores of greater than 4 at more than one time point during the study. There were no statistical comparisons performed between groups. There were no clear differences in the reported degree of difficulty swallowing between the two treatment groups.

Harms (Safety and Tolerability)

- In the RP103-03 study, seven patients (16%) experienced an SAE and six of these patients reported the SAE during treatment with delayed-release cysteamine. SAEs reported during treatment with delayed-release cysteamine included abdominal discomfort, vomiting, hypokalemia, gastroenteritis, femur fracture, and knee deformity. One patient reported an SAE of hypovolemia during treatment with immediate-release cysteamine.
- Overall, 58% and 32% of patients reported adverse events during treatment with delayed-release cysteamine and immediate-release cysteamine, respectively.

- Gastrointestinal adverse events were the most frequently reported category of adverse event and were reported in 14 patients (33%) during treatment with delayed-release cysteamine and in nine patients (22%) during treatment with immediate-release cysteamine. Of the more frequently reported adverse events, patients reported nausea (16%), vomiting (19%), and abdominal pain (9%) during treatment with delayed-release cysteamine, compared with 7%, 12%, and 0%, during treatment with immediate-release cysteamine, respectively.
- The incidence of non-gastrointestinal adverse events in the study was 26% (11/43) during treatment with delayed-release cysteamine and was 10% (4/41) during treatment with immediate-release cysteamine.
- Body odour and bad breath were identified by patient groups as adverse events of concern related to immediate-release cysteamine treatment. A subgroup analysis of the RP103-03 study was performed that hypothesized that delayed-release cysteamine would be associated with less severe halitosis due to dimethylsulfide in the breath. The subgroup analysis showed non-statistically significant decreases in breath dimethylsulfide during treatment with delayed-release cysteamine, compared with breath levels taken during treatment with immediate-release cysteamine (n = 4, *P* = 0.068 for area under the curve of dimethylsulfide levels). Patients' personal experiences of halitosis in this subgroup analysis were not assessed.

Cost and Cost-Effectiveness

At the manufacturer's submitted price ($11.30 per 25 mg capsule, $33.89 per 75 mg capsule), the daily cost of delayed-release cysteamine will vary from $373 in a two-year-old child (based on a body surface area of 0.63 m^2) to $881 in adults (based on a body surface area of 1.50 m^2), resulting in an annual cost ranging from $136,000 to $321,000 per patient.

The manufacturer submitted a cost-utility analysis comparing delayed-release cysteamine to no treatment for the treatment of nephropathic cystinosis in a population of two-year-old children initiating treatment. The analysis was undertaken from the perspective of the Canadian health care payer with a lifetime horizon (100 years). In the model, patients with nephropathic cystinosis could experience disease complications due to nephropathic cystinosis such as diabetes, end-stage renal disease (ESRD), and neuromuscular disorders. Given the paucity of data comparing delayed-release cysteamine in relation to no treatment, a retrospective study of cystinosis patients in Europe, which compared patients on immediate-release cysteamine (no longer available in Canada) and untreated patients, supplemented by clinical expert opinion (one expert) was used to inform comparative clinical efficacy. The manufacturer's clinical expert estimated that delayed-release cysteamine, through better adherence to treatment, could further delay ESRD by five years and survival by 13 years compared with immediate-release cysteamine. These values were compared with data from the untreated patients in the retrospective study to inform the comparison against no treatment.

CDR identified some key limitations with the manufacturer's analysis. The assumption of better clinical outcomes for delayed-release cysteamine compared with immediate-release cysteamine based on feedback from one clinical expert as a result of better adherence to treatment was not appropriate. Given the importance of this parameter in the model, anecdotal evidence provided by one expert was not an appropriate method to justify this assumption and may have overestimated the magnitude of benefit associated with delayed-release cysteamine. The dose of delayed-release cysteamine used by the manufacturer in the analysis was lower than the recommended dose, especially noting the up-titration of delayed-release cysteamine in the submitted clinical trial.

CDR re-analyses, which included a more conservative assumption for the clinical efficacy for delayed-release cysteamine, revised dosing of delayed-release cysteamine to better align with the product monograph, revised utility values for the baseline health state, neuromuscular complications, and revised complication costs, which resulted in an incremental cost-utility ratio (ICUR) of $1,124,329 per QALY. The magnitude of treatment effect and cost of delayed-release cysteamine were the key drivers of the results. While delayed-release cysteamine may increase life expectancy compared with no treatment, it is also associated with a high rate of complications since patients live longer, which increases the total health care costs. At a 95% reduction in the price of delayed-release cysteamine, the ICUR remained above $100,000 per QALY compared with no treatment.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 13, 2017 Meeting

Regrets:

Two CDEC members did not attend.

Conflicts of Interest:

None