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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Cysteamine delayed-release capsules (Procysbi)

Horizon Pharma Ireland Ltd.

Indication: For the treatment of nephropathic cystinosis

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Abbreviations

CE	cost-effectiveness
EQ-5D-Y	EuroQol5-Dimension-Y (Youth)
ESRD	end-stage renal disease
HTA	Health Technology Assessment
ICUR	incremental cost-utility ratio
LY	life-year
LYG	life-year gain
MS	multiple sclerosis
nmol	nanomoles
PD	Parkinson's disease
PE	pharmacoeconomic
PedsQL 4.0	Pediatric Quality of Life Inventory version 4.0
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SE	standard error

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Delayed-release cysteamine capsules (Procysbi)
Study Question	What are the anticipated costs and health consequences of the use of cysteamine delayed-release for the treatment of nephropathic cystinosis when compared with no treatment?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with nephropathic cystinosis
Treatment	Cysteamine delayed-release
Outcomes	LYs QALYs
Comparator	No treatment (complication management only)
Perspective	Canadian health care system
Time Horizon	Lifetime (100 years in a 2-year-old child)
Results for Base Case	$675,605 per QALY (deterministic)
Key Limitations	• The magnitude of the incremental benefit of delayed-release cysteamine compared with no treatment is uncertain due to the lack of comparative evidence. • The assumption of improved effectiveness for delayed-release cysteamine compared with immediate-release cysteamine is based on expert opinion is not supported by a head-to-head noninferiority study comparing the two treatments (RP103-03). • The assumption that complications due to the condition (i.e., diabetes, end-stage renal disease, neuromuscular disorders, and death) were independent of one another is an oversimplification of the model structure. Several complications are known to be interdependent, which may alter the time to the onset of these complications. This could not be assessed in the submitted economic model. • The disutility value for neuromuscular disorders was overestimated. • The dose of delayed-release cysteamine does not represent the dose recommended in the product monograph. • Methodological limitations were noted with regard to how uncertainty was tested in the model (relevant parameters were not tested in the probabilistic analysis or inadequate distributions tested).
CDR Estimate(s)	CADTH undertook revisions to the submitted model based on identified limitations. • The number of iterations in the probabilistic analyses was increased to 5,000. • The dose of delayed-release cysteamine was assumed to align with the product monograph recommended dose and the standard deviation was revised to reflect the variability observed in study RP103-03. • The efficacy of delayed-release cysteamine was revised to be equivalent to that of immediate-release cysteamine. • Different disutilities and costs for neuromuscular disorders were used, as well as a different baseline utility value. These changes led to the CADTH base-case ICUR being $1,124,329 per QALY. A price reduction of more than 95% is required for the ICUR to be less than $100,000 per QALY.

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.

Indication	Treatment of nephropathic cystinosis
Reimbursement Request	As per indication
Dosage Form(s)	Delayed-release 25 mg and 75 mg capsules
NOC Date	13 June 2017
Manufacturer	Horizon Pharma Ireland Ltd.

Executive Summary

Background

Cysteamine (Procysbi), a delayed-release formulation containing 25 mg or 75 mg of cysteamine bitartrate (referred to as delayed-release cysteamine) was approved by Health Canada for the treatment of patients with nephropathic cystinosis.[1] Cystinosis is a recessive autosomal genetic ultra-rare disease affecting 1 in 100,000 to 200,000 live births in Europe (1 in 62,500 in Saguenay-Lac-St-Jean, Quebec),[2,3] characterized by renal and extrarenal (i.e., diabetes, osteopenia, muscular weakness and wasting, growth retardation, etc.) complications. Cysteamine acts through preventing or delaying the occurrence of renal and extrarenal complications and hence prolonging life expectancy.[4-7] The recommended dose of delayed-release cysteamine is 1.3 g/m^2 daily to be given in two equal doses per day. At the manufacturer's submitted price ($11.30 per 25 mg capsule, $33.89 per 75 mg capsule), the daily dose cost will vary from $372.90 in a two-year-old child (based on a body surface area of 0.63 m^2) to $881.40 in adults (based on a body surface area of 1.50 m^2), or $136,000 to $321,000 per patient annually.[8]

An immediate-release formulation (immediate-release cysteamine) was previously available in Canada through a Health Canada Special Access Programme. However, this program was ended by Health Canada in late October 2017, and the immediate-release formulation is no longer available.

The manufacturer submitted a cost-utility analysis comparing delayed-release cysteamine to no treatment in children and adults with nephropathic cystinosis. Based on a population of two-year-old children who start treatment (the safety and efficacy of delayed-release cysteamine in patients under two years of age have not been established),[1] a time horizon of 100 years (lifetime) was considered. The analysis was undertaken from the perspective of the Canadian health care payer. The model structure considered patients moving from a baseline health state at diagnosis (i.e., two years old with nephropathic cystinosis) to developing disease complications due to nephropathic cystinosis such as diabetes, end-stage renal disease (ESRD), and neuromuscular disorders. Due to the lack of long-term information on the comparative efficacy of delayed-release cysteamine in relation with no treatment, the manufacturer relied on a retrospective study of cystinosis patients in Europe which compared patients on immediate-release cysteamine and those who were untreated patients. As the impact of delayed-release cysteamine on the age at complication onset, as well as on treatment adherence has not been studied, the manufacturer used expert opinion (one expert) to estimate these values for the economic model.[8] The expert estimated that

delayed-release cysteamine, through better adherence to treatment, could further delay ESRD by five years and increase survival by 13 years in comparison to immediate-release cysteamine. These values were compared with data from the untreated patients in the retrospective study to inform the comparison against no treatment. Other inputs such as costs and utility values were obtained from published literature.

The manufacturer estimated in their base case that delayed-release cysteamine could result in an additional 12.98 quality-adjusted life-year (QALYs) and an incremental cost of $8,770,005, resulting in an incremental cost-utility ratio (ICUR) of $675,605 per QALY when compared with no treatment (deterministic analysis).

Summary of Identified Limitations and Key Results

The main limitations with the manufacturer's analysis were the lack of clinical information on the benefit of delayed-release cysteamine compared with no treatment, and how the cost of delayed-release cysteamine was calculated.

The manufacturer's comparison of delayed-release cysteamine compared with no treatment was appropriate given the status of immediate-release cysteamine in Canada. However, clinical information to inform this comparison was based on data from a retrospective study which assessed cystinosis patients treated with immediate-release cysteamine or who were not treated. The manufacturer suggested better clinical outcomes for delayed-release cysteamine compared with immediate-release cysteamine based on feedback from one clinical expert who believed delayed-release cysteamine would delay the occurrence of complications due to nephropathic cystinosis compared with immediate-release cysteamine as a result of better adherence to treatment. 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 overestimate the magnitude of benefit associated with delayed-release cysteamine. As reported in the manufacturer's randomized controlled trial (RP103-03), delayed-release cysteamine had similar efficacy to immediate-release cysteamine which raises further speculation with regards to the comparative clinical benefit of delayed-release cysteamine.

CADTH also noted that the dose of delayed-release cysteamine used by the manufacturer in the analysis was lower than the recommended dose. Given the available dosing information, and the noted uptitration of delayed-release cysteamine in the RP103-03 trial, the product monograph recommended dose is more likely to be a more appropriate estimate.

CADTH noted other important limitations with the model. Certain utility values and costs used in the model were not likely to be representative for Canadian patients with cystinosis. Additionally, uncertainty was not incorporated appropriately in the model (e.g., low number of model iterations; limited parameters were tested in the probabilistic analysis; distributions around the mean value did not adequately test expected variance).

CADTH reanalyses, 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 and neuromuscular complications, and revised complication costs resulted in an ICUR of $1,124,329 per QALY. The cost of delayed-release cysteamine is the key driver of the cost-effectiveness of delayed-release cysteamine. While delayed-release cysteamine may increase life expectancy, this also results in a high rate of complications as patients live longer, increasing the total health care costs. At a 95% reduction in the price of delayed-release cysteamine, the ICUR remains above $100,000 per QALY compared with no treatment.

Conclusions

The manufacturer's analysis has several limitations, the most important being the assumption taken on the efficacy of delayed-release cysteamine. Based on CADTH reanalyses, the ICUR is likely to be $1,124,329 per QALY compared with no treatment. Even at a price reduction of 95%, the ICUR remains greater than $100,000 per QALY compared with no treatment.

At the submitted price, the annual cost of delayed-release cysteamine will vary between $136,109 for a 2-year-old child to $321,711 for an adult.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a Markov model (which used components of a partitioned survival model and was referred to as a "Markov partitioned survival model" by the manufacturer) comparing delayed-release cysteamine to no treatment in patients with nephropathic cystinosis. A lifetime time horizon (100 years) was considered for the starting population of 2 year old children with nephropathic cystinosis. The analysis was conducted from the perspective of the Canadian health care payer, with costs and clinical outcomes (QALYs and life-years) discounted at 1.5% per annum.

The following health states were included in the Markov model: no complication; end-stage renal disease (ESRD); diabetes; neuromuscular disorders; any combination of two complications, three complications, and death. The manufacturer used a retrospective study in a cohort of 86 nephropathic cystinosis patients diagnosed in France in the years 1961 to 1995 as the basis for treatment effectiveness (time to event).[9] In the retrospective cohort, 75 of the 86 patients (87%) received immediate-release cysteamine (40 patients started treatment before age 5; 8 patients started treatment after age 5, but prior to developing ESRD; and 27 patients only started treatment once ESRD was established, i.e., at 22.6±5.7 years). Eleven (11) patients never received cysteamine. The retrospective study was used to provide estimations of the patient age at which death and complications (ESRD, diabetes, neuromuscular disorder) occur in untreated patients. The impact of delayed-release cysteamine on the time to death or complication has not been empirically measured and limited to the short duration noninferiority trial.[10] The manufacturer used expert opinion to estimate the impact of delayed-release cysteamine in comparison to immediate-release cysteamine for the time to which events might occur, i.e., ESRD, diabetes, neuromuscular disorders, and death. In the retrospective cohort study, untreated patients developed ESRD at a median age of 9 years, while patients who started immediate-release cysteamine before age 5 developed ESRD at a median age of 15 years (or 6 years later). The manufacturer consulted a clinical expert who believed that delayed-release cysteamine can further delay ESRD by another 5 years (or 11 years later than in the untreated patients). More details of the manufacturer's assumptions regarding the efficacy of delayed-release cysteamine can be found in Appendix 5. Time to death or complication was estimated from hazard ratios using a Weibull distribution, which then informed the transition probabilities used in the Markov model.

Costs and utilities were derived from the literature and are used in an aggregated form for the base case, i.e., one single value is used throughout the years where this complication is present. In sensitivity analyses, the manufacturer adds some more details to the costs and utilities, in particular for ESRD where the impact of kidney transplant and dialysis modalities is taken into accounts for costs and utilities.

The manufacturer's base-case analysis was deterministic. Parameter uncertainty was assessed through probabilistic sensitivity analysis (PSA) and structural uncertainty through scenario analyses.

Manufacturer's Base Case

In the base case, the manufacturer estimated the incremental costs associated with delayed-release cysteamine compared with no treatment to be $8,770,005 with an incremental quality-adjusted life-year (QALY) gain of 12.98 and an incremental life-year gain (LYG) of 16.36 years over the lifetime of a patient. The resulting incremental cost-effectiveness ratios were $675,605 per QALY or $536,168 per LYG (based on a deterministic analysis). Results from the manufacturer's base case are shown in Table 2.

Table 2: Summary of Results of the Manufacturer's Base Case (Deterministic Analysis)

	Total Costs	Incremental Cost	Total LYs	Incremental LYs	Total QALYs	Incremental QALYs	Incremental Cost per QALY
Delayed-release cysteamine	$9,531,676	$8,770,005	34.47	16.36	27.46	12.98	$675,605
No treatment	$761,671		18.11		14.48		

LY = life-year; QALY = quality-adjusted life-year.

The manufacturer performed a PSA on some of the main parameters (i.e., patient age at event occurrence; costs: disease complications, treatment, adverse events, patient management; utilities). The ICUR from the PSA was recalculated from the manufacturer's pharmacoeconomic submission, which can be calculated as $679,382 per QALY. According to the manufacturer's analysis, 95% of the iterations are found to be between $562,277 and $860,714 per QALY.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer performed a series of scenario analyses to test the structural uncertainty of the model (75% and 50% of children initiating treatment below age 5; time horizon at 60 years; exclusion of diabetes and neuromuscular disorder as complications; using 0.80 as baseline utility value rather than 0.95; using a 'micro-tariff' for ESRD utility and costs). The manufacturer presented only the results of the deterministic analyses. The lowest ICUR ($612,497 per QALY) resulted from a scenario where diabetes and neuromuscular complications were excluded. On first consideration, this result may appear counterintuitive. While costs were only slightly lower than in the base case ($8,702,504 versus $8,770,005) (likely due to the exclusion of diabetes and neuromuscular disorder management costs), the QALY gain was higher (14.21 versus 12.98). The manufacturer does not provide an explanation for this result. Looking at the results in detail, when excluding diabetes and neuromuscular disorders from the calculations, more QALYs accumulated over time and, as patients in the delayed-release cysteamine group live longer, the difference in QALY accumulation between the two groups grows over time.

The highest ICUR ($821,927 per QALY) resulted from a scenario where only 50% of the children initiated treatment below the age of five years.

Limitations of Manufacturer's Submission

The key limitations identified with the manufacturer's analysis primarily pertain to the amount and quality of clinical evidence available:

- **Lack of clinical evidence comparing delayed-release cysteamine with no treatment:** While the manufacturer considered the appropriate comparator in the economic evaluation, no treatment (as immediate-release cysteamine will not be available to Canadian patients with the introduction of delayed-release cysteamine), comparative evidence against delayed cysteamine is lacking. The pivotal clinical trial presented by the manufacturer examines delayed-release cysteamine with immediate-release cysteamine (RP103-03). In order to derive the natural history for patients without treatment, the manufacturer considered information from a retrospective cohort study which assessed the natural history of untreated patients. Within this cohort, 86 adults (15 years old and above) in whom nephropathic cystinosis had been diagnosed between 1961 and 1995 in France received immediate-release cysteamine.[9] The base treatment effect for delayed-release cysteamine was based on data from patients receiving immediate-release cysteamine in the retrospective cohort study; however, an additional benefit was assumed for delayed-release cysteamine compared with immediate-release cysteamine. This was based on feedback from one clinical expert (author of the retrospective cohort study) who indicated patients receiving delayed-release cysteamine would live an additional 13 years and the onset of the noted complications would be delayed by between two and 10 years (see Appendix 5 for additional details). These assumptions of additional benefit did not align with the results of the RP103-03 trial.

  As all patients in Canada diagnosed with nephropathic cystinosis are currently treated with immediate-release cysteamine, it may have been more appropriate to consider patients with a baseline health state equivalent to immediate-release cysteamine.

- **Assumptions regarding the comparison of delayed-release cysteamine with immediate-release cysteamine:** The manufacturer's clinical expert based their opinion on the potential for better adherence to treatment with delayed-release cysteamine, which may result in lower levels of leukocyte ½ cystine. Feedback from a clinical expert consulted by CADTH indicated that levels of leukocyte ½ cystine less than 1 nmol/mg protein are used in current Canadian practice. This is lower than the ½ cystine level reported in the retrospective study, which was associated with less frequent ESRD in cystinosis patients (less than and equal to 3 nmol/mg protein).[9] In the retrospective study, the adherence to treatment for patients with immediate-release cysteamine was considered as being 'good or quite good' by the treating physician in 75.9% of patients (no further explanation of the rating was given in the publication). Any overestimation of the efficacy of delayed-release cysteamine will bias the results in favour of delayed-release cysteamine.

  Expert knowledge elicitation was not performed according to current best practices, especially in view of the importance of the elicited parameter in the analysis.[11,12] This increases the uncertainty in the model and limits assessing the impact of this uncertain value on the model results.

  The RP103-03 trial found that delayed-release cysteamine was noninferior to immediate-release cysteamine for efficacy parameters. However, CADTH noted that there was a higher proportion of serious and non-serious adverse events for patients in the delayed-release cysteamine group compared with the immediate-release cysteamine group, thus there may be some uncertainty with the comparative harms associated with the treatments.

- **Dose of delayed cysteamine:** In the model, the dose of delayed-release cysteamine used was lower than the dose recommended in the product monograph (1.3 g/m2 daily). The manufacturer indicated the lower dose is appropriate based on the dose intensity in the RP103-03 trial. In the RP103-03 trial, patients in the delayed-release cysteamine group received on average 1,513 ± 477 mg/day (however a dose based on body surface area was not presented). CADTH noted that while patients on delayed-release cysteamine received 70% of the dose of immediate-release patients at the start of the study, the average dose over the course of the trial was 84% of the dose of immediate-release cysteamine. Using a different dose has an immediate impact on treatment cost.

Other limitations:

- **Assumptions regarding the clinical condition:** The manufacturer assumed that complications and survival are independent of each other. This is an oversimplification, as the impact of diabetes or kidney failure on survival and health care costs is well documented.[13-17] Thus, the chosen modelling approach limits the possibility of assessing the impact of delayed-release cysteamine on survival, if delayed-release cysteamine has a greater impact on one complication over the other. For example, if the impact of delayed-release cysteamine is greater on diabetes than on kidney failure, the model might overestimate the impact on survival. A model that considered the complications interdependently would have been more appropriate.
- **Utility values.** Most utilities used in the model were approximated from the literature and may not represent the actual value for the health state. Details on how the values were transformed prior to being used in the model (e.g., utilities transformed into disutilities, costs inflated to 2017, aggregated costs and disutilities) were not clearly detailed. In several cases, however, more appropriate sources (e.g., Canadian patients rather than Canadian health care workers) or values (in relation to a healthy cohort rather than crude values) would have been preferable. These utilities were combined by using the multiplicative method, which, although being the most appropriate method of combining utility values, is less preferable compared with full health state values, as combining values increases the uncertainty on the size of the benefit of delayed-release cysteamine. When the manufacturer combined utilities using the multiplicative method, the manufacturer assumed perfect health as the base value when determining the disutility to apply, however studies have shown that correcting for population norms when matched controls are not available gives more accurate results.[18]
- **Multiple sclerosis (MS) as a proxy for neuromuscular disorder:** The manufacturer used MS as a proxy for neuromuscular disorders both for utilities and costs. The clinical expert consulted by CADTH suggested that Parkinson's disease (PD) may represent a better proxy as the myopathy in nephropathic cystinosis patients as there is cumulative deterioration in PD, rather than being relapsing-remitting as most common in MS. CADTH tested values from PD in the revised base case.
- **Assumptions regarding treatment adherence:** The manufacturer assumed that treatment adherence with delayed-release cysteamine is 100% over the lifetime. A survey of cystinosis patients (or parents of patients) showed that treatment adherence to immediate-release cysteamine decreases as the patient grows older.[19] It would have been more realistic to consider a less-than-perfect adherence to treatment. Although the model allows for testing other treatment adherence values, this change only affects drug costs and does not impact efficacy. CADTH was unable to assess the impact of adherence on the efficacy of treatment based on the submitted model.
- **Assumptions regarding transplant and dialysis:** The manufacturer used transplant and dialysis data (e.g., waiting time for kidney transplant, proportion of peritoneal dialysis versus hemodialysis) from Canadian adults, although the first kidney transplant for cystinosis patients is expected to happen at around age nine in the untreated group. Average waiting time for a kidney transplant in children is much shorter than in adults (18 months versus 47.3 months); furthermore, peritoneal dialysis is more frequently used in children than adults (54% versus 22.7%).[20,21] These two elements would reduce the costs of ESRD, in particular in no treatment and thus, increase the overall incremental costs and ICUR. In addition, if children receive a kidney transplant earlier, survival would also be affected, reducing QALY gain and increasing the ICUR. The clinical expert consulted by CADTH noted that the time to starting any renal replacement modality would be a better outcome measure of disease progression (i.e.,: time to start dialysis, hemodialysis, or that a child receiving a pre-emptive renal transplant [bypassed dialysis]).
- **Model is only partially probabilistic:** The structure of the model does not allow to fully testing uncertainty. Only a small subset of the model parameters is included in the PSA

to test parameter uncertainty. The model does not properly reflect the fact that in children, the waiting time to kidney transplant is shorter and that peritoneal dialysis is more frequently used than hemodialysis.

- Only 2,000 iterations were done in the PSA, as opposed to the 5,000 recommended in CADTH guidelines.[22]

Further details and additional limitations can be found in the reviewers' worksheets in Appendix 5.

CADTH Common Drug Review Reanalyses

CADTH considered the following revisions to the submitted model to form the CADTH Common Drug Review (CDR) base case:

- Increase the number of probabilistic iterations to 5,000 to be consistent with CADTH guidelines.
- Adjust delayed-release cysteamine dose standard deviation to 31.5% of the dose (based on data from the RP103-03 study) to better reflect variability in dose.
- Adjust delayed-release cysteamine dose to the dose recommended in the product monograph, i.e., 1,300 mg/m^2 (rather than 1,083 mg/m^2).
- Reduce the efficacy of delayed-release cysteamine to that of immediate-release cysteamine.
- Use a different set of utilities and costs for neuromuscular disorders and the baseline as described in Appendix 5.

The ICUR in CADTH base case increased to $1,124,329 per QALY from the manufacturer base case of $676,126 per QALY. The largest ICUR increases (in decreasing order) came from setting the delayed-release cysteamine efficacy to that of immediate-release cysteamine, changing the dose to the product monograph recommended dose and setting the baseline utility.

Summary results are found in Table 3 and detailed results can be found in Appendix 5.

Table 3: Summary of CADTH Reanalysis (Probabilistic Analysis)

	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
Delayed-release cysteamine	$8,732,065	$7,982,782	20.27	7.10	$1,124,329
No treatment	$749,283		13.17		

Note: The probabilistic analysis was not structured to report life-years.
QALY = quality-adjusted life-year.

CADTH undertook price reduction analyses on the CDR base-case analysis and manufacturer's submitted probabilistic analysis (2,000 iterations) in Table 4. Even with a 95% price decrease, the CDR base case ICUR is still above $100,000 per QALY. One explanation for this is that as patients live longer with cysteamine, the number of patients living with a kidney transplant or being on dialysis also increases. ESRD represents a large part of the costs in these patients (98.1% of the total costs in the no-treatment group). The model estimates a $330,297 (lifetime 1.5% discounted costs) increase in ESRD costs in the delayed-release cysteamine group. Other incremental costs in the delayed-release cysteamine group include routine monitoring of ½ cystine levels (+$40,085) and

neuromuscular disorders (+$7,226). The only complication for which costs are more or less stable even if the patients live longer is diabetes.

CADTH also noted that at a 99% price reduction on the manufacturer's submitted probabilistic analysis (2,000 iterations), the ICUR was not below $50,000 per QALY.

Table 4: Summary of CADTH Price Reduction Analysis

Price	Manufacturer's Probabilistic Analysis ($ per QALY)	CADTH Base Case ($ per QALY)
Submitted	679,382	1,124,329
20% reduction	555,065	895,424
40% reduction	427,301	689,405
60% reduction	302,208	476,967
80% reduction	174,697	263,904
90% reduction	112,314	159,505
92% reduction	**99,336**	NR
96% reduction	NR	**95,487**
99% reduction	55,357	63,672

NR = not reported; QALY = quality-adjusted life-year.

Issues for Consideration

Prior to the availability of delayed-release cysteamine, immediate-release cysteamine was the standard of care for nephropathic cystinosis patients in Canada. Immediate-release cysteamine was only available through Health Canada Special Access Programme which ended in late October 2017. The annual medication cost was estimated to be $2,515 to $5,450 per year, as per the price of immediate-release cysteamine listed on the Newfoundland and Labrador formulary website (Table 5).[23] There is substantial uncertainty as to whether patients will be able to access treatment in the interim, outside of accessing delayed-release cysteamine through special access.

Feedback from the clinical expert consulted by CADTH noted that as immediate-release cysteamine requires more frequent dosing – including a dose in the middle of the night – doses are missed by patients. The delayed-release formulation requires a lower administration burden on the patient, though there is a greater pill burden, due to the size of the capsules available.

Patient Input

Input from 82 patients with nephropathic cystinosis (or their caregiver) was obtained through the Canadian Organization for Rare Disorders. Sixty-two per cent of the respondents were from Canada, 28% from the US and 5% from elsewhere. Of those who had taken or were currently taking immediate-release cysteamine, comments were made on the following: although it greatly improves patient's condition, cysteamine does not resolve all the clinical manifestations of the disease; adherence to the strict six-hour schedule; breath and skin odour as well as digestive side effects; the amount of pills to be taken.

There is hope that delayed-release cysteamine will resolve some of these challenges (e.g., dosing regimen, side effects), patients are concerned by the high cost of treatment.

Delayed-release cysteamine is unlikely to address several of these concerns; in particular, the number of pills to be taken will be greater with delayed-release cysteamine as it is only available in 25 mg and 75 mg capsules, compared with 150 mg capsules with immediate-release cysteamine. The 12-hour schedule should be seen as an improvement over the strict 6-hour schedule, especially that this medication is to be taken by children and over the lifetime. Breath and skin odour as well as digestive effects are expected to be addressed by delayed-release cysteamine; however, no firm evidence exists at this moment. The price of delayed-release cysteamine is high and accessibility to the medication will certainly be a challenged for some patients.

Conclusions

The manufacturer's analysis has several limitations, the most important being the assumption taken on the efficacy of delayed-release cysteamine. Based on CADTH reanalyses, the ICUR is likely to be $1,124,329 per QALY compared with no treatment. Even at a price reduction of 95%, the ICUR remains more than $100,000 per QALY compared with no treatment.

At the submitted price, the annual cost of delayed-release cysteamine will vary between $136,109 for a 2 years old child to $321,711 for an adult.

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 Table 5 and as such may not represent the actual costs to public drug plans.

Table 5: CDR Cost Table for Cysteamine Delayed-Release

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Delayed-release cysteamine	25 mg 75 mg	capsules	$11.30[a] $33.89[a]	1,300 mg/m^2/day	2 yrs old (825 mg): $372.90 5 yrs old (1,025 mg): $463.30 10 yrs old (1,375 mg): $621.50 15 yrs old (1,750 mg): $791.00 Adult (1950 mg): $881.40	$136,108.50 in a 2-year-old child to $321,711.00 in an adult
Previously available treatments –through Health Canada Special Access Programme						
Immediate-release cysteamine	150 mg	capsules	$1.148[b]	1,300 mg/m^2/day	2 yrs old (900 mg): $6.89 5 yrs old (1,050 mg): $8.04 10 yrs old (1,350 mg): $10.33 15 yrs old (1,800 mg): $13.78 Adult (1950 mg): $14.92	$2,515.84 in a 2-year-old child to $5,450.99 in an adult

[a] Manufacturer submitted price.[24]
[b] Newfoundland and Labrador Department of Health and Community Services. Reported as $574.04 per 500 tablets. [23]
m^2 = metres squared; mg = milligrams; yrs = years.

Appendix 2: Summary of Key Outcomes

Table 6: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Delayed-Release Cysteamine Relative to No Treatment?

Delayed-Release Cysteamine vs. No Treatment	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$1,124,329 per QALY (CADTH results)					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 7: Submission Quality

Are the methods and analysis clear and transparent?			X
Comments	As inflation adjustments are not done in the model, it is difficult to assess which values have been used from the sources and whether inflation adjustment has been properly applied. In general, the methods are not very detailed and required a lot of time to understand how calculations were done. There are several errors in the way sources are used, in particular for resources and costs. The ESRD 'micro-costing' is not operational in the no-treatment group in the model provided to CADTH.		
Was the material included (content) sufficient?		X	
Comments	Study report RP103-03 does not include calculation of baseline EQ-5D		
Was the submission well organized and was information easy to locate?		X	
Comments	See above regarding retrieval of information from data sources used in the model. Furthermore, the manufacturer did not provide the analysis on the PedsQL 4.0 transformation into a utility.		

EQ-5D = EuroQol5-Dimension; ESRD = end-stage renal disease; PedsQL 4.0 = Pediatric Quality of Life Inventory version 4.0.

Table 8: Author Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ 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	

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

Note: Cysteamine delayed-release capsules have only been reviewed by the French Haute Autorité de Santé (HAS).[25]

	HAS (23 September 2015)
Treatment	Cysteamine 25 mg and 75 mg delayed-release capsules
Price	Not available
Similarities to CDR submission	Study submitted: 1. RP103-03 (noninferiority trial against immediate-release cysteamine) 2. RP103-04 (follow-up study)[26,27] 3. Publications on immediate-release cysteamine[9,28,29] NOTE: According to HAS report, study RP103-7 and RP103-8 were ongoing at time of review
Differences from CDR submission	No cost-effectiveness analysis
Manufacturer's results	Not applicable
Issues noted by the review group	Limited information on the efficacy of delayed-release cysteamine. Digestive adverse events were more frequent with delayed-release cysteamine; however, the protocol restricted the use of proton pump inhibitors in the delayed-release cysteamine group but not in the immediate-release cysteamine group. Treatment adherence was not assessed in the trial and although patient quality of life was recorded, results are too limited to allow any conclusion. Therefore, no effect above and beyond immediate-release cysteamine is expected.
Results of reanalyses by the review group (if any)	Not applicable
Recommendation	SMR[a] rating: Important ASMR[b] rating: IV (minor improvement versus immediate-release cysteamine) NOTE: Immediate-release cysteamine has been available in France since 1998 and was given an ASMR rating of I (major) as it was the first medication for the disease

[a] SMR: service medical rendu (medical benefit).
[b] ASMR: amelioration du service medical rendu (medical benefit improvement [over currently available options]).
CDR = CADTH Common Drug Review; HAS = Haute Autorité de Santé.

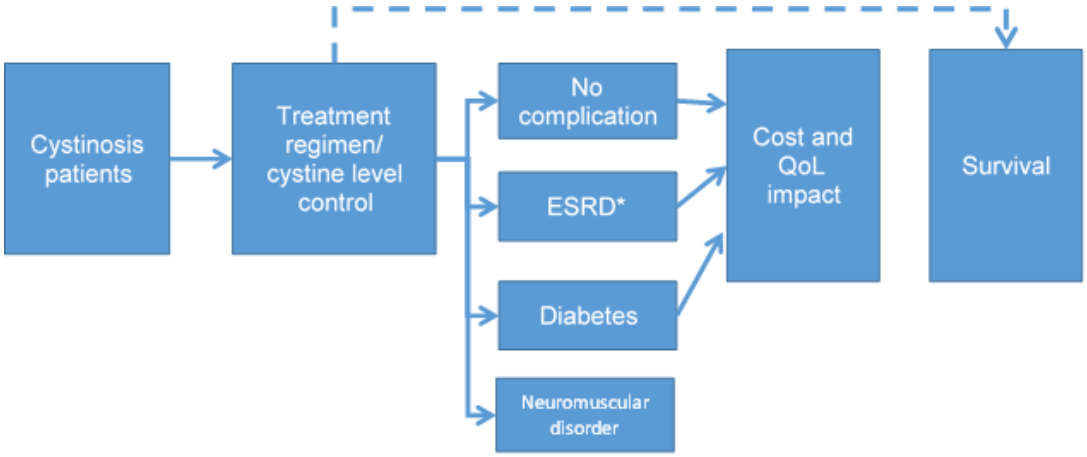
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a partitioned survival model comparing delayed-release cysteamine to no treatment. Cysteamine is the only specific treatment existing for nephropathic cystinosis in Canada. The manufacturer noted that a short-acting formulation (immediate-release cysteamine) was available through a federal special access program, although this was to be stopped upon the entry of delayed-release cysteamine to the Canadian market.

The manufacturer considered a lifetime horizon (i.e., 100 years in 1-year cycles with half-cycle correction) in a two-year-old child with cystinosis. The analysis adopted the Canadian public health care payer perspective with an annual discount rate of 1.5% on health benefits and costs. In addition to death, three different complications are followed throughout the model: end-stage renal disease (ESRD), diabetes, and neuromuscular disorder, with the possibility for patients to have no complication, only one complication, any combination of two complications, or three complications. The model structure as presented by the manufacturer can be seen in Figure 1.

Figure 1: Model Structure



ESRD = end-stage renal disease; QoL = quality of life.
Source: Manufacturer's Pharmacoeconomic Submission.[8]

The manufacturer used a retrospective study in a cohort of 86 nephropathic cystinosis patients diagnosed in France in the years 1961 to 1995 as the basis for the time to events.[9] In this retrospective cohort, 75 of the 86 patients (87%) received the short-acting formulation of cysteamine (40 patients started treatment before age five years; eight patients started treatment after age five years, but prior to any complications; and 27 patients only started treatment once ESRD was established, i.e., 22.6 ± 5.7 years). Eleven (11) patients never received cysteamine. Therefore, this retrospective study provides estimation of the time to events (death, ESRD, diabetes, neuromuscular disorder) in untreated patients as well as those starting cysteamine short-acting before age five years and after age five years.

The median age of onset for the three modelled complications, and death, as derived from the Brodin-Sartorius study[9] for immediate-release cysteamine are provided in Table 9.

Empirical data on the long-term impact of delayed-release cysteamine are not available. The manufacturer consulted a clinical expert (Dr. Brodin-Sartorius) who noted that as compliance was only reported as good for 35% of patients and quite good for 41% of patients, there may be additional patient benefits associated with delayed-release cysteamine due to the side effect profile, compliance, early diagnosis, and monitoring. The revised estimates based on feedback from the clinical expert are also provided in Table 9. The manufacturer stated that monitoring and subsequent control of ½ cystine levels (and general health) have improved over the intervening years.

Table 9: Median Patient Age at Complication Onset Used in the Model

Event	Untreated[9]	Immediate-Release Cysteamine (Starting Age < 5) (Yrs)[9]	Assumption For Delayed-Release Cysteamine (Starting Before Age 5) (Yrs)	Difference Between Delayed-Release Cysteamine And Untreated (Yrs)	Difference Between Delayed-Release Cysteamine And Immediate-Release Cysteamine (Yrs)
ESRD	9	15	20	11	5
Diabetes	15	38	40	25	2
Neuromuscular disorder	25	35	45	20	10
Death	23	37	50	27	13

ESRD = end-stage renal disease; yrs = years.
Source: Manufacturer's Pharmacoeconomic Submission[8]

In the model, these data were considered through hazard ratios using a Weibull distribution, which was modelled to allow the manufacturer to transform these to different probabilities that patients would be in each Markov health state.

Table 10: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Risks for complications and mortality in the no-treatment group were taken from a retrospective cohort study with immediate-release cysteamine.[9] Assumptions on the superiority of delayed-release cysteamine compared with immediate-release cysteamine were based on expert opinion.	The assumption of incremental effectiveness of delayed-release cysteamine compared with immediate-release cysteamine is based on the opinion of one expert, and is not supported by published evidence. The expert based his opinion on the potential for better adherence to treatment with cysteamine delayed-release. Some of the reasons given by the expert (e.g., early diagnosis and monitoring) are unlikely to have an impact as these changes in practice have occurred independently of effects from cysteamine therapy. Expert opinion on this important parameter was not obtained through state-of-the-art methodology.[11,12] Feedback from the clinical expert consulted by CADTH indicated that the biologic plausibility of the assumption of an incremental benefit of delayed-release cysteamine compared with immediate-release cysteamine is rational; greater adherence will hopefully lead to delayed morbidity. However the magnitude of the incremental benefit, if any, is not known. Therefore, the assumption of equivalent effectiveness in the model is acceptable.
Natural history	Risk of complications and mortality based on a retrospective cohort study [9]	The efficacy of cysteamine is based on a retrospective study where immediate-release cysteamine was used in 86 adults. Only 11 individuals were in the untreated

Data Input	Description of Data Source	Comment
		cohort for the survival analysis. For diabetes and neuromuscular disorders, the cohorts were more or less equal. It is uncertain whether the small number of patients in the untreated group and each subgroup were sufficient for the statistical comparisons. As most of the comparisons were based on hypothesis tests with *P* values; standard errors and confidence intervals were not reported. Thus, it is difficult to evaluate the precision and the clinical relevance of the statistical findings.
Utilities	Disutilities of adverse events, and complications from the medical literature.	In general, it is unclear which values have been used from the cited sources and how disutilities were calculated from the utilities reported in the sources. More specifically: • The diabetes value reported in Dale's systematic review[30] comes from a time-trade-off study in 17 Canadian health care workers. Utilities in Canadian diabetes patients can be found in the literature. • The manufacturer's used MS as a proxy for neuromuscular disorders. According to the clinical expert consulted by CADTH, PD would be more appropriate; while MS may come and go with different severity, PD is cumulative in terms of deterioration, which more closely resembles this complication. Furthermore, utilities were rarely tested in the PSA.
	Baseline utility for a child with cystinosis from mapping of PedsQL 4.0 collected at month 1 in Langman's study (40 children; average age 11.5 years).[31]	The PedsQL 4.0 values from the RP103-03 study[31] transformed into utilities via an algorithm were inflated by the manufacturer, i.e., from 0.873 to 0.95 on the basis that study patients were rather sick, and this would not be representative of a 2-year-old child starting on treatment. No norm is available yet from the EuroQol group on the EuroQol5-Dimension-Y (EQ-5D-Y).[32] However, a Canadian study in (likely healthy) 3,421 Grade 5 students (i.e., aged 11-12 years old, as per Langman's study) reported an average EQ-5D-Y index score of 0.86.[33] Utilities mapped from quality of life questionnaires are not recommended for Health Technology Assessment.[22] Even the author of the PedsQL mapping algorithm noted the variance in prediction accuracy across the range of fitted EQ-5D-Y utility scores.[34] Furthermore, the UK tariffs were used for the development of the algorithm. Using the Canadian tariff set might give different results. PedsQL 4.0 values not published in Langman's article[31]and the manufacturer has not provided a report of their analysis.
Resource use	Treatment information from RP103-03 trial (assuming no dropout)	Dose in RP103-03 trial is lower than recommended dose from product monograph
	ESRD: dialysis modalities and waiting time to transplant from CORR[20,21] Time to graft failure from medical literature	The manufacturer used data from adults to populate dialysis modality usage and waiting time for kidney transplant. However, as the age at which ESRD is established is estimated to be 9 years in the no-treatment group, it would have been more appropriate to also use the information from children. There are differences

Data Input	Description of Data Source	Comment
		between adults and children in the usage of peritoneal dialysis (54% in children vs. 22.7% in adults age 20 to 44 years) and waiting time for a kidney transplant (18 months in children vs. 47.3 months in adults).[20,21] This could impact the costs and QALYs. Van Stralen reports 17.9% hemodialysis, 39.6% peritoneal dialysis, 35.1% transplant, 7.5% unknown in starting the renal replacement therapy modality in patients with cystinosis.[35]
Adverse events	Gastric acid production in 10.4% of patients (source: RP103-03 study) managed by proton pump inhibitors	Feedback from the clinical expert consulted by CADTH suggested clinicians are moving away from proton pump inhibitors due to their potential impact on kidney function. H2 blockers are the alternative.
Mortality	From medical literature[9]	Data are limited (86 patients) relatively old (diagnosis between 1961 and 1995) and from France only, hence questionable generalizability to Canadian setting.
Costs		
Drug	Cost of delayed-release cysteamine provided by the manufacturer	Appropriate
Administration	No administration costs	Oral formulation. Note that recommended dosage represents 10 to 26 capsules per day
Event	ESRD: base case uses an aggregated value from a paper published in 2007 but reporting in 2000 $CAD[36] This paper obtained its estimated from various sources, including the medical literature and Ontario medical fee schedule. The manufacturer uses a so-called 'micro-costing' approach in the sensitivity analyses where a cost for hemodialysis, peritoneal dialysis, kidney transplant first year, and kidney transplant subsequent year are used.	The ESRD cost estimates for the base case are old and would have benefited from more recent values and better adaptation to the children population. For example, the 2000 CORR data used for this estimate reports 22% on peritoneal dialysis while in children the proportion was 54% in the 2016 report.[20,21] The ESRD 'micro-costing' is not operational in the no-treatment group in the version of the model provided to CADTH.
	Diabetes costs from medical literature (study in Ontario)[37]	It is difficult to understand which value of the publication has been used for the model as the publication reports different values for each year after diagnosis for men and women.
	Cost for neuromuscular disorders from medical literature[38]	Although the source uses Canadian data (Ontario and BC), the costs are for MS patients.[38] Feedback from the clinical expert consulted by CADTH suggested that PD would be a better proxy than MS for neuromuscular disorders due to the progressive nature of the disease.
	Routine care: MD visit: $38.05 (Ontario); hemicystine test: $342 (US$ value converted to C$ using 1.35 rate)	US dollar to Canadian dollar conversion rate is higher than the current exchange rate. The ½ cystine test can be done in Canada; however, CADTH was not able to find a public price.
		The manufacturer reports inflation-adjusted values in the submitted pharmacoeconomic report.[8] Adjustments for inflation are not included in the model, aggregate values are presented. Therefore, it is difficult to validate which value has been used from the source and if inflation adjustment has been done properly. Greater transparency should have been provided.

Data Input	Description of Data Source	Comment
		Note that manufacturer estimates standard error for PSA as 0.10 or 0.25 of average cost depending on cost rather than using 95% confidence interval.
Adverse events	Proton pump inhibitor $11.54 per month (ODB)	According to the clinical expert consulted by CADTH, clinicians are moving away from proton pump inhibitors due to their potential impact on kidney function. H2 blockers are the alternative. However, this value has very limited impact on the ICUR.
Health state	No complication ESRD Diabetes Neuromuscular disorder Any combination of 2 of these 3 complications Death	Feedback from the clinical expert consulted by CADTH confirmed that these are the most important complications in this patient population.

CORR = Canadian Organ Replacement Registry; EQ-5D-Y (Youth) = EuroQol5-Dimension-Y; ICUR = incremental cost-utility ratio; ESRD = end-stage renal disease; MS = multiple sclerosis; ODB = Ontario Drug Benefit; PD = Parkinson's disease; PedsQL 4.0 = Pediatric Quality of Life Inventory version 4.0; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Table 11: Manufacturer's Key Assumptions

Assumption	Comment
Patients were assumed to enter the model at 2 years of age.	This is appropriate based on the product monograph which notes that the safety and efficacy of delayed-release cysteamine in patients under 2 years of age have not been established. However, for the model information was provided as to whether the patients entering at 2 years of age had existing disease or whether these were newly presenting patients.
Survival partition approach assumes the risks of complications and mortality are independent of each other.	This is a simplification of the reality as the impact of diabetes or kidney failure on survival is well documented. Therefore, the chosen modelling approach limits the possibility of assessing the impact of delayed-release cysteamine on survival if the product was to have a greater impact on one complication over another. For example, if the impact of cysteamine is greater on kidney failure than on diabetes, the model might underestimate the impact on survival. Furthermore, when survival equations are independent of each other, care must be taken in sensitivity analyses to avoid logical fallacy (i.e., time to a complication is longer than time to death).[39] Feedback from the clinical expert consulted by CADTH highlighted the interdependent nature of the complications of cystinosis.
Risks of complications and death are conditional on the age when cysteamine therapy started (i.e., Brodin-Sartorius shows that treatment before the age of 5 years leads to improved outcomes compared with treatment starting after the age of 5 years).	In the Brodin-Sartorius study,[9] the size of the 3 cohorts varies according to the complication. For example, for ESRD, the cohort starting after age 5 consists of only 8 patients. For death, there are only 11 untreated patients. Therefore, some of these subgroups are very small and even if a statistically significant difference were observed, the statistical power might be low. For example, no difference is seen for ESRD incidence between starting after age 5 and not starting before reaching ESRD, however, only 8 patients started after age 5. For diabetes, neuromuscular disorders, and death, starting after age 5 was much closer to the 'starting before age 5' curves. The 'after age 5' group was bigger in all cases (n = 17 for diabetes; n = 28 for neuromuscular disorders; n = 35 for death)

Assumption	Comment
Model projections over a lifetime are beyond the observed follow-up time.	Acceptable
The risk estimates are predicted based on assumptions for the shape of the long-term hazard function for each event (i.e., Weibull or Gompertz).	The shape of the distribution for a survival function is often Weibull or Gompertz, the ones used by the manufacturer; however, a better approach would have been to test various functions and choose the most appropriate.[40]
Quality of life values were based on an analysis of trial outcomes, then mapped using a published algorithm.	Utilities mapped from quality of life questionnaires are not recommended for Health Technology Assessment.[22]
The impact of delayed-release cysteamine on median time to complications is from the opinion of one single expert.	Although the expert consulted by the manufacturer is the author of the natural history paper and has experience using immediate-release cysteamine, his opinion was based on assumptions regarding the side effect profile, patient compliance, and monitoring of delayed-release cysteamine. This assumption highly increases the uncertainty around the estimates.
The routine care of cystinosis and management of complications are assumed to have no overlap with each other.	Acceptable
The micro-costing and micro-tariff approach for mean ESRD cost and tariff is based on the assumption that post-ESRD survival of all patient categories would follow an exponential distribution.	Reasonable. However, the micro-costing and micro-tariff approach was not used by the manufacturer in their base case, and was not programmed in the notreatment group in the version of the model provided to CADTH.
It is appropriate to use time to transplant as a marker of disease activity.	This is complicated by the fact that when a patient is deemed ready for transplant, there may not be a donor. Feedback from the clinical expert consulted by CADTH indicated that the wait time is influenced by a variety of factors, including donor availability, health of the recipient, HLA matching and sensitization (i.e., previous exposure to blood antigens affecting the ease of finding an HLA-matched donor). It was also indicated that children may preferentially receive peritoneal dialysis more than adults due to factors limiting hemodialysis use in a small body.
The curves of age of complication onset and age of death for different patient categories are assumed to share the same curve shape.	Acceptable
The Kaplan–Meier curves in the Brodin-Sartorius et al. study (Figure 2) represent complication free with death considered as an event.	This is unlikely the case. The survival curve referenced by the manufacturer likely represents the overall survival in all 86 patients, some of them with 1 or more complications.
Maximum of 2 kidney transplants over the lifetime.	Reasonable. A US study showed that 42 out of 100 patients received a second transplant.[28]

ESRD = end-stage renal disease; HLA = human leukocyte antigen; n = number of patients in subgroup.

Manufacturer's Results

The manufacturer's base case estimates the incremental expenses to using delayed-release cysteamine at $8,770,005 over the lifetime of a patient with an incremental quality-adjusted life-year (QALY) gain of 12.98 and an incremental life-year gain (LYG) of 18.11 years. The resulting incremental cost-utility ratio (ICUR) is $675,605 per QALY or $536,168 per LYG (deterministic analysis). Table 12 below reproduces the manufacturer's results.

Table 12: Manufacturer's Base Case Results (Deterministic Analysis)

	Delayed-Release Cysteamine	No Treatment	Incremental
Total average cost	$9,531,676	$761,671	$8,770,005
Cost of drug treatment for cystinosis	$8,144,642	$0	
Cost of routine management	$55,018	$4,134	
ESRD costs	$1,239,937	$733,000	
Diabetes costs	$11,346	$7,275	
Neuromuscular disorder costs	$80,692	$17,262	
Adverse event costs	$41	$0	
LYs	34.47	18.11	16.36
QALYs	27.46	14.48	12.98
Incremental cost per LY gained			$536,168
Incremental cost per QALY gained			$675,605

ESRD = end-stage renal disease; LY = life-year; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission[8]

The ICUR from the probabilistic sensitivity analysis (PSA) has been recalculated from Table 12 of the manufacturer's pharmacoeconomic submission by dividing the average incremental costs by the average incremental QALY (i.e., $8,784,414/12.93). This gives an ICUR of $679,382. Also to be noted, only 2,000 iterations have been included in the PSA. According to the manufacturer's analysis, 95% of the iterations are found between $562,277 and $860,714 per QALY.

The manufacturer produced a series of scenario analyses (0% and 3% discounting; 75% and 50% of children initiating treatment below age of five years; time horizon at 60 years; exclusion of diabetes and neuromuscular disorder as complications; using 0.80 as baseline utility value rather than 0.95; using a 'micro-tariff' for ESRD utility). Only results of the deterministic analyses were presented in the manufacturer's report. The lowest ICUR ($612,497 per QALY) was seen with the scenario where diabetes and neuromuscular complications were excluded. This is a little counterintuitive. While costs were only slightly lower ($8,702,504 versus $8,770,005 in the base case), QALY gain was higher (14.21 versus 12.98 in the base case). The highest ICUR ($821,927 per QALY) was seen in the scenario where only 50% of the children initiated treatment below the age of five years. Costs were lower ($7,012,105 versus $8,770,005 in the base case), and so was the QALY gain as well (8.53 versus 12.98 in the base case).

CADTH identified the following limitations with the manufacturer's model in addition to those listed in the main body of the report:

- There is an option to use 'micro-costing' for ESRD in the submitted model. While this can be applied for the delayed-release cysteamine group, it is not able to be applied to the no-treatment group. Although the use of the micro-costing approach would have been more appropriate, the manufacturer did not apply this appropriately to allow an accurate assessment of the cost-effectiveness when 'micro-costing' is selected.
- The variance around the values could not always be identified in the cited sources or was generated through questionable methods (e.g., average divided by four for several cost values). This is particularly important for the clinical efficacy where the standard error was 0.05 for all parameters.

CADTH Common Drug Review Reanalyses

Two publications estimating the cost-effectiveness of immediate-release cysteamine were found in the literature.[41,42] One, published as an abstract only, reported the cost-effectiveness of cysteamine in Poland.[41] The other, published as a full paper, reported a cost-consequence analysis in the US setting.[42] Both models were decision trees focusing on renal complications only. Cysteamine was assessed as being cost-effective in the Polish analysis, but the publication format (i.e., abstract only), does not allow full appraisal of the analysis. In the US analysis, incremental costs were estimated at $4,000 over the patient lifetime for an incremental survival of 5.5 years. This was based on annual immediate-release cysteamine costs of $1,600 per year (likely 1996/1997 costs). In comparison, delayed-release cysteamine annual costs are estimated to be $136,109 and $321,711 based on recommended dose and body surface area. Therefore, these analyses do not provide a lot of insight to the current submission.

In view of the limitations of the manufacturer's base case noted above, CADTH undertook a series of reanalyses to determine the CADTH base case:

- Increase PSA iterations to 5,000 to be consistent with CADTH guidelines
- Adjust cysteamine delayed-release dose standard deviation to 31.5% of dose (using the relationship between standard deviation of the daily dose and daily dose in the RP103-03 study as a proxy) to account for variability in dose
- Adjust cysteamine delayed-release dose to the product monograph recommended dose, i.e., 1,300 mg/m^2 (rather than 1,083 mg/m^2)
- Reduce the efficacy of delayed-release cysteamine to that of immediate-release cysteamine
- Use a different set of utilities and costs for neuromuscular disorders and the baseline (Table 13).

The literature was reviewed to identify more appropriate inputs in particular for utilities and costs. Preference was given to recent Canadian values. CADTH inputs are listed in Table 13.

Table 13: CADTH Base Case Inputs Compared With Manufacturer's Inputs

Parameter	Manufacturer's Value [SE]	Manufacturer's Source	CADTH Value [SE]	CADTH Source
Clinical[a]				
Time to ESRD	HR vs. no treatment: 0.83 [0.05] Untreated: 9 yrs Cysteamine: 20 yrs	Brodin-Sartorius[9] and expert elicitation	HR: 1.00 [0.05] Untreated: 9 yrs Cysteamine: 15 yrs	Brodin-Sartorius[9]
Time to diabetes	HR: 0.93 [0.05] Untreated: 15 yrs Cysteamine: 40 yrs	Brodin-Sartorius[9] and expert elicitation	HR: 1.00 [0.05] Untreated: 15 yrs Cysteamine: 38 yrs	Brodin-Sartorius[9]
Time to neuromuscular disorder	HR: 0.89 [0.05] Untreated: 25 yrs Cysteamine: 45 yrs	Brodin-Sartorius[9] and expert elicitation	HR: 1.00 [0.05] Untreated: 25 yrs Cysteamine: 35 yrs	Brodin-Sartorius[9]
Death	HR: 0.11 [0.05] Untreated: 23 yrs Cysteamine: 50 yrs	Brodin-Sartorius[9] and expert elicitation	HR: 1.00 [0.05] Untreated: 23 yrs Cysteamine: 37 yrs	Brodin-Sartorius[9]

Parameter	Manufacturer's Value [SE]	Manufacturer's Source	CADTH Value [SE]	CADTH Source
Utilities or disutility				
Neuromuscular disorder[b]	–0.32 [0.05]	Karampampa[43]	–0.22 [0.04]	Pohar[44]
Baseline utility	0.95 [0.05]	Study RP103-03[10]	0.860 [0.0025]	Wu[33]
Costs and health care resources				
Neuromuscular disorders	$17,993 per year [mfr value divided by 4]	Amankwah[38]	$3,104 Sampling performed on number of hospitalizations in PD (2.30 [0.10]) and control patients (2.10 [0.09]). Inpatient PD costs: $15,521 [$1,285]) per case	Hobson[45] for hospitalizations. OCCI for inpatient costs
Cysteamine daily dose	1,083 mg/m^2 [50]	Study RP103-03[10]	1,300 mg/m^2 [410]	Manufacturer submission[24]

[a] The manufacturer is using a 'Hazard Ratio' as a multiplier used to adjust the survival curves of the short-acting formulation from Brodin-Sartorius' publication[9] to reflect the assumptions on the delayed-release formulation

[b] Disutility: negative value

ESRD = end-stage renal disease; HR = hazard ratio; mfr = manufacturer; m^2 = metre squared; mg = milligram; OCCI = Ontario Case Costing Initiative; PD = Parkinson's disease; SE = standard error; yrs = years.

Table 14: CADTH Reanalysis: Base Case Details (Probabilistic Analysis)

Scenario	Element		Total Cost	Total QALY	ICUR
CADTH base case:	5,000 iterations	Delayed-release cysteamine	$9,558,609	27.5043	
		No treatment	$759,460	14.4902	
		Incremental analysis	$8,799,149	13.0141	$676,126
	Dose standard error changed to 31.5% of dose	Delayed-release cysteamine	$9,559,847	22,4317	
		No treatment	$760,541	14.4658	
		Incremental analysis	$8,799,306	12.9658	$678,653
	Dose changed to product monograph recommended dose, i.e., 1,300 mg/m^2/day	Delayed-release cysteamine	$11,205,210	27.4147	
		No treatment	$761,318	14.4675	
		Incremental analysis	$10,443,892	12.9472	$806,655
	Efficacy similar to short-acting formulation	Delayed-release cysteamine	$8,724,302	22.1341	
		No treatment	$761,861	14.4575	
		Incremental analysis	$7,962,441	7.6766	$1,037,235
	Utility for neuromuscular disorder changed to –0.22 [0.04]	Delayed-release cysteamine	$8,710,132	22.4375	
		No treatment	$759,846	14.5715	
		Incremental analysis	$7,950,285	7.8661	$1,010,705
	Baseline utility changed to 0.860 [0.0025]	Delayed-release cysteamine	$8,706,370	20.2849	
		No treatment	$760,177	13.1620	
		Incremental analysis	$7,946,193	7.1230	$1,115,576
	Neuromuscular disorder costs	Delayed-release cysteamine	$8,732,065	20.2680	
		No treatment	$749,283	13.1679	
		Incremental analysis	$7,982,782	7.1000	$1,124,329

ICUR = incremental cost-utility ratio; m^2 = metres squared; mg = milligram; QALY = quality-adjusted life-year.

Sensitivity on the price of delayed-release cysteamine was performed (Table 4 and Table 15). A price reduction of more than 95% was necessary to bring the ICUR below $100,000 per QALY. An analysis of the impact on various cost items showed that a large part of the costs associated with delayed-release cysteamine treatment is related to the management of ESRD. Although delayed-release cysteamine delays the incidence of ESRD, by increasing the survival, it also increases the risk of patients developing ESRD or other complications. In the CADTH base case, ESRD costs totalled $733,000 (98.1% of the total costs) in the untreated cohort. In the delayed-release cysteamine group, ESRD costs increased to $1,063,297. Similar increases were seen for neuromuscular disorders, while diabetes costs were stable. Even when the price of delayed-release cysteamine were reduced by 95%, the total costs were twice as high in the delayed-release cysteamine group as in the no-treatment group, with increased ESRD costs being responsible for 50% of the increase in total costs.

Table 15: CADTH Reanalyses: Additional Price Reduction Analysis

Scenario	Element		Total Costs	Total QALY	ICUR
Scenario 1:	Base case	Delayed-release cysteamine	$8,732,065	20.2680	
		No treatment	$749,283	13.1679	
		Incremental analysis	$7,982,782	7.1000	$1,124,329
	25% price reduction	Delayed-release cysteamine	$6,786,525	20.2685	
		No treatment	$745,439	13.1625	
		Incremental analysis	$6,041,087	7.1060	$850,139
	50% price reduction	Delayed-release cysteamine	$4,893,737	20.2621	
		No treatment	$744,824	13.1539	
		Incremental analysis	$4,148,913	7.1081	$583,685
	75% price reduction	Delayed-release cysteamine	$2,997,932	20.2937	
		No treatment	$740,366	13.1687	
		Incremental analysis	$2,257,565	7.1251	$316,847
	95% price reduction	Delayed-release cysteamine	$1,501,616	20.2748	
		No treatment	$744,718	13.1704	
		Incremental analysis	$756,898	7.1044	$106,540

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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