Common Drug Review
Pharmacoeconomic Review Report

April 2017

Drug	asfotase alfa (Strensiq)
Indication	Enzyme replacement therapy in patients with a confirmed diagnosis of pediatric-onset hypophosphatasia (HPP)
Listing request	As per indication
Dosage Form	Solution for subcutaneous injection (40 mg/mL and 100 mg/mL single-use vial)
NOC Date	NOCc (with conditions) issued August 2015
Manufacturer	Alexion Pharma Canada Corp.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in pediatrics who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

6MWT	six-minute walk test
BSC	best supportive care
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
EQ-5D-5L	EuroQol 5-Dimensions 5 Levels Questionnaire
HPP	hypophosphatasia
ICUR	incremental cost-utility ratio
MCID	minimal clinically important difference
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Asfotase alfa (Strensiq)
Study Question	To evaluate the incremental costs and benefits of asfotase alfa versus BSC in patients with pediatric-onset HPP
Type of Economic Evaluation	CCA
Target Population	Patients with pediatric-onset HPP
Treatment	Asfotase alfa, 1 mg/kg subcutaneous injection 6 times per week or 2 mg/kg subcutaneous injection 3 times per week
Outcomes	QALYs
Comparator	BSC, defined as the need for surgical interventions, hospitalizations, intensive care unit services, respiratory assistance, outpatient visits, consultations, and pain medication
Perspective	Canadian publicly funded health care system
Time Horizon	Lifetime (101 years)
Results for Base Case	Incremental cost of asfotase alfa versus BSC: $27,728,012 Incremental benefit of asfotase alfa versus BSC: 10.27 QALYs
Key Limitations	• The manufacturer did not calculate a base-case ICUR, which complicates the interpretation of the results • Uncertainty regarding the use of the 6MWT to model disease progression, given that this end point has not been assessed and validated as an appropriate surrogate outcome to correlate with disease severity and progression in HPP • Substantial limitations with the 6MWT data used for modelling due to the design, context, and generalization of the studies collecting these data and the subsequent need for predictive modelling for select patient age subgroups where these data are not available • Uncertainty regarding the long-term efficacy of asfotase alfa • Uncertainty around the methodology used to derive utility weights • Inappropriate assumption regarding the future costs of asfotase alfa, where the manufacturer assumed that at year 10, loss of data exclusivity would lead to a 30% decrease in the list price of asfotase alfa • Manufacturer assumed no costs associated with the wastage of partially used vials of asfotase alfa

CDR Estimates	The ICUR based on the disaggregated results reported by the manufacturer was calculated by CDR to be $2.7 million per QALY. CDR conducted a number of reanalyses to assess the impact of several of the limitations identified.
	• A reanalysis assuming the price of asfotase alfa stays constant in the future (i.e., no reduction in price) and including the cost of wastage of partially used vials of asfotase alfa resulted in an ICUR of $4.08 million per QALY (CDR reference case).
	• Considering the above CDR reference case:
	  ○ Altering the utility weights (based on their confidence intervals) resulted in ICURs of $4.02 million and $8.83 million per QALY when lower and higher values were used, respectively.
	  ○ Stratifying by severity, the ICUR ranged from $3.62 million per QALY for the patients with the most severe presentation (severity level IV) to $4.34 million per QALY for patients with the least severe presentation (severity level I).

[redacted]	○ Stratifying by patient age at the start of the model, the ICUR ranged from $2.28 million per QALY for patients who start at birth to $12.83 million per QALY for patients who start after the age of 18 years. ○ The CDR analyses suggest that the cost-effectiveness of asfotase alfa is more favourable in patients who have more severe disease and are treated at an earlier age (ICUR is $2.29 million per QALY for patients who have severe disease and initiate treatment at birth). However, the model structure allows the assessment of different patients' subgroups with restriction, when considering that HPP is a highly variable disease in terms of symptoms and clinical manifestations, at different ages, onset of disease, and treatment.

6MWT = six-minute walk test; BSC = best supportive care; CCA = cost consequence analysis; CDR = CADTH Common Drug Review; HPP = hypophosphatasia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.

EXECUTIVE SUMMARY

Background

Asfotase alfa is being reviewed as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of pediatric-onset hypophosphatasia (HPP).[1] The recommended dose is 2 mg/kg of body weight three times per week or 1 mg/kg of body weight six times per week, administered subcutaneously.[1] Asfotase alfa is available in two concentrations — 40 mg/mL and 100 mg/mL — and in various single-use vial doses: 18 mg, 28 mg, or 40 mg for 40 mg/mL; and 80 mg for 100 mg/mL. The manufacturer submitted a price of $102.00 per mg,[2] which corresponds to annual cost of approximately:

- $286,416 for patients weighing between 0 kg and 9 kg
- $445,536 for patients weighing between 10 kg and 14 kg
- $636,480 for patients weighing between 15 kg and 20 kg
- $1,272,960 for patients weighing between 21 kg and 40 kg
- $2,545,920 for patients weighing between 41 kg and 80 kg.

The manufacturer is seeking reimbursement in line with the Health Canada indication.

A cost-utility analysis was submitted comparing asfotase alfa with best supportive care (BSC, defined as the need for surgical interventions, hospitalizations, intensive care unit services, respiratory assistance, outpatient visits, consultations, and pain medication) using data from four clinical trials (ENB-002-08, and its extension ENB-003-08; ENB-006-09, and its extension ENB-008-10; ENB-009-10; and ENB-010-10)[3-6] and two natural history studies (ENB-011-10 and ALX-HPP-502).[7,8] The reference case time horizon was lifetime (101 years), considering the Canadian publicly funded health care system perspective. The economic submission was based on a Markov model with four key health states defined primarily by the severity level of disease. This was quantified by the observed over the predicted six-minute walk test (6MWT) score, where the predicted score was determined based on age, gender, and height normative data. Other health states included death by HPP and background death, and an invasive ventilator toll state.[2] The manufacturer considered the severity of HPP to be age-dependent, and as such, calculated age-specific transition probabilities.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the submitted model. The manufacturer did not report a base-case incremental cost-utility ratio (ICUR), but reported the results disaggregated by costs and benefits (quality-adjusted life-years [QALYs]), which complicates the interpretation. Additionally, there is uncertainty regarding the use of the 6MWT as a surrogate end point to model disease progression, as its correlation with disease severity has not been clearly assessed in HPP. This led the manufacturer to use data from another disease (Duchenne muscular dystrophy) to structure its model, which is limiting. In addition, the design, context, and generalization of the studies collecting 6MWT data and the subsequent need for predictive modelling for select patient age subgroups where these data are not available lead to substantially limiting its use. Other limitations included the uncertainty regarding the long-term efficacy of asfotase alfa, the uncertainty in the methodology used to derive utility weights, the inappropriate assumption around the future cost of asfotase alfa, and the assumption that there were no costs associated with wastage of partially used vials.

CDR calculated an ICUR of $2,698,950 per QALY from the manufacturer's results. A reanalysis of the limitations surrounding the future cost of asfotase alfa (i.e., no reduction in price) and accounting for the cost of wastage of partially used vials resulted in an ICUR of $4,080,555 per QALY. Considering the latter as the CDR reference case, altering the utility weights based on the extreme values defined by the confidence intervals results in ICURs of $4,018,632 and $8,828,056 per QALY, when lower and higher values are used, respectively. Further, using the CDR reference case, stratifying by disease severity results in an ICUR of $3,616,563 per QALY for the most severe state (severity level IV) to $4,343,087 per QALY for the least severe state (severity level I). When stratifying by baseline patient age, the ICUR ranges from $2,276,483 per QALY for patients who start treatment at birth to $12,834,335 per QALY for patients who start treatment after the age of 18. As such, treatment with asfotase alfa is more cost-effective in patients who have a higher severity of disease and are treated at any earlier age (using the CDR reference case, the ICUR was calculated to be $2,291,707 per QALY for patients in the most severe health state treated at birth). However, the model structure allows only the assessment of different patient subgroups with restriction, when considering that HPP is a highly variable disease in terms of symptoms and clinical manifestations, at different ages, and onset of disease and treatment.

Conclusions

Based on the manufacturer's submitted economic evaluation, CDR calculated the ICUR for asfotase alfa when compared with BSC to be approximately $2.7 million per QALY. CDR reanalysis addressing limitations regarding the costs resulted in a significant increase to the ICUR to $4.08 million per QALY, which could be even higher given the substantial uncertainty associated with the model. Asfotase alfa appears to be most likely cost-effective in patients who are in a more severe health state and are treated at birth ($2.29 million per QALY).

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing asfotase alfa (Strensiq) to best supportive care (BSC, defined as the need for surgical interventions, hospitalizations, intensive care unit services, respiratory assistance, outpatient visits, consultations, and pain medication) in patients diagnosed with pediatric-onset hypophosphatasia (HPP).[2] The analysis was conducted under the Canadian publicly funded health care system perspective.[2]

The model consists of six health states, four of which were defined by the severity level of disease, based on the observed over the predicted six-minute walk test (6MWT) score; death by HPP; and death by other causes. Invasive ventilator is also included as a toll state (i.e., a temporary health state associated with disutility and additional costs). In the manufacturer's base case, patients entered the model at an age of 5.8 years at any of the severity health states, and transitioned between these states every 12 weeks over a lifetime time horizon (101 years).[2] The health states and the baseline distribution were defined as follows (based on 28 patients for whom there were 6MWT data available, from studies ENB-006-09/ENB-008-10 and ENB-009-10):[4,5]

- Severity level I: (observed 6MWT/predicted 6MWT) > 82.2% (22.2 % of patients)
- Severity level II: 82.2% ≥ (observed 6MWT/predicted 6MWT) > 64.4% (33.3% of patients)
- Severity level III: 64.4% ≥ (observed 6MWT/predicted 6MWT) > 46.6% (29.6 % of patients)
- Severity level IV: (observed 6MWT/predicted 6MWT) > 46.6% or those who could not complete the 6MWT (14.8% of patients)
- HPP-related death (0% of patients)
- Background death, not related to HPP (0% of patients)
- Invasive ventilator toll state (0% of patients).

In the model, patients progress between severity health states and can transition to death or the invasive ventilator toll state at any time point. As there were no severity categories based on the 6MWT outcome in HPP, the manufacturer defined the severity levels using an approach previously used in patients with Duchenne muscular dystrophy,[2,9] although there is no clear evidence to support this. In the manufacturer's analysis, the severity of HPP was considered to be age-dependent. The probability of transitioning between severity states was based on 6MWT data from 28 patients who received asfotase alfa or BSC. These data were obtained from the following open-label, phase II clinical trials assessing asfotase alfa with a historical or no-treatment concurrent control (where 6MWT was an exploratory or secondary outcome): ENB-006-09 and its extension (ENB-008-10), which assessed patients aged five to 12 years; and ENB-009-10, which assessed patients aged 13 to 66 years.[4,5] The manufacturer estimated an ordered probit regression model that allowed for the calculation of age-specific transition probabilities, based on 6MWT data from the above-mentioned trials, allowing for predictions for patients younger than five years and older than 65 years for whom 6MWT data are not available. Additionally, when a patient is in the invasive ventilator toll state, the manufacturer assumed a health utility decrement and additional direct medical costs. Furthermore, all patients who require an invasive ventilator were assumed to transition to the most severe health state afterward (severity level IV). The transition probabilities for HPP-related death and the invasive ventilator health state were taken from the following studies assessing patients younger than five years: asfotase alfa studies ENB-002-08 and its

extension (ENB-003-08), and ENB-010-10; and a natural history study, ENB-011-10.[3,6,7] In the manufacturer's base case (where patients started at 5.8 years old), the probability of transitioning into the HPP-related death or the invasive ventilator health state was 0% after the age of five years, as both of these outcomes were not observed past the age of four in the trials.

The manufacturer conducted a utility elicitation study to determine utility weights for each of the health states. In summary, case histories were created based on two natural history studies (ENB-011-10 and ALX-HPP-502).[7,8] These case histories were then summarized into descriptions of the health states, with input from clinical experts. Following this, the clinical experts were asked to rank each description in order of severity, as related to the 6MWT, and then rate each of the descriptions using the EuroQol 5-Dimension 5 Levels Questionnaire (EQ-5D-5L).

Resource utilization was determined by estimating the frequency of clinical events expected in addition to the background care level needed for each of the health states, with input from a clinical expert. Costs information was primarily obtained from the Ontario Schedule of Benefits for Physician Services (2015),[10] among other sources.[2] The manufacturer assumed that the cost of wastage associated with partially used vials of asfotase alfa would not be incurred by the publicly funded health care system, although nothing was stated regarding who would incur this cost. Additionally, the manufacturer assumed that 10 years from the start of the model, loss of data exclusivity will lead to a 30% decrease in the list price of asfotase alfa.[2]

2. MANUFACTURER'S BASE CASE

The manufacturer reported that the total cost associated with treatment with asfotase alfa was $28,338,582, an incremental cost of $27,728,012 compared with BSC. Further, treatment would result in 16.53 quality-adjusted life-years (QALYs), an incremental QALY gain of 10.27 compared with BSC. As the manufacturer assumed there would be no benefits in terms of survival after five years and that the base case assumed a patient starting age of 5.8 years, the incremental QALY gain with treatment with asfotase alfa is in this case entirely based on benefits in morbidity, which represents an important difference in patient severity state over the patient lifetime. The CADTH Common Drug Review (CDR) calculated the incremental cost-utility ratio (ICUR) to be $2,698,950 (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE-CASE ANALYSIS, PER PATIENT

	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	ICUR
Best supportive care	$610,570	$27,728,012	6.26	10.27	$2,698,950
Asfotase alfa	$28,338,582		16.53		

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty regarding the parameters chosen for the base-case analysis was addressed by the manufacturer by conducting scenario analyses, one-way deterministic sensitivity analyses, and a probabilistic sensitivity analysis. As noted in Table 11 below in Appendix 4, when stratified by patient

age, the highest QALY gain was reported in patients diagnosed at birth (and who commenced treatment at that time), and the ICUR increased as patient age increased.
The following parameters had the greatest impact on the ICUR (± 25%): use of higher utility values; use of an alternate model specification (where different covariate variables were considered in the calculation of transition probabilities); low and high discount rate for costs and QALYs; and variation of the threshold values that define the severity states.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Uncertainty regarding the use of the 6MWT to model disease progression**: Although the manufacturer may have used the best approach given the available evidence, there is substantial uncertainty that the outcome of 6MWT is appropriate in terms of a surrogate end point to appropriately predict the evolution and the severity of HPP. There is uncertainty as to whether it captures all important symptoms and manifestations of the disease, and further, how it relates to resources use and benefits in terms of health-related quality of life. Additionally, the manufacturer defined and structured its model in term of disease severity based on the assessment and validation of the 6MWT and related minimal clinically important difference (MCID) values in patients with Duchenne muscular dystrophy,[2,9] which further increases the uncertainty of the approach.
- **Limitations of using 6MWT data from the clinical trials to model disease progression**: The 6MWT data were collected as exploratory or secondary outcomes from studies that included patients from the ages of five to 65 years (ENB-006-09/ENB-008-10 and ENB-009-10).[4,5] Thus, predictive modelling was necessary to model disease severity and progression for patients below and above that range, as these data were not available. Additionally, 6MWT data were from open-label studies with a historical or no-treatment concurrent control, and as such, the comparative efficacy value of asfotase alfa versus BSC is limited by the design of these studies, and by the fact that there were substantial differences between the control and treatment arms in terms of baseline characteristics (see CDR Clinical Review report). Moreover, 6MWT data were collected from only 28 patients, which limits the generalization of the findings. Finally, study ENB-009-10 (which assessed patients aged 13 to 66 years) did not use the approved dosage of asfotase alfa but a lower one, which limits its use in this context and biases the results from the perspective of a cost-effectiveness assessment.
- **Uncertain long-term efficacy of asfotase alfa:** The limited availability of long-term data (beyond five years) with asfotase alfa introduces substantial uncertainty regarding its comparative cost-effectiveness versus BSC in the long term. Although the manufacturer assumed varying transition probabilities based on age, under the assumption that disease evolution is age-dependent, the manufacturer also assumed that the treatment response observed in the clinical trials would maintain for the duration of the entire time horizon. There is no evidence to confirm that the efficacy of asfotase alfa is maintained over time. Additionally, if asfotase alfa affects the evolution of disease differently based on age and time of treatment initiation, the effect of treatment would differ according to patient age, profile, and disease characteristics and the generalization of the effect of the treatment in the long term becomes limited. The model illustrates that patients treated with asfotase alfa would mostly be in the mildest disease severity state for their lifetime (utility weight of 0.86), as compared with patients treated with BSC, which was illustrated in the model by patients mostly being in the most severe disease severity state for their lifetime (utility weight of 0.23). This was the case for most types of patient profiles initiating treatment in the model, which is questionable.
- **Uncertainty regarding the methodology used to derive utility weights:** The manufacturer derived health utility estimates by asking clinical experts to map patient profiles (determined based on case

histories created from the natural history studies, ENB-011-10 and ALX-HPP-502)[7,8] to 6MWT values, followed by summarizing into descriptions of each health state, and then rating them using the EQ-5D-5L. There is a high degree of uncertainty associated with this approach. These descriptions may not fully reflect the outcomes experienced by patients in a given health state, especially with a disease such as HPP, where there is a substantial range of symptoms or clinical manifestations of the disease. Further, as mentioned by the manufacturer, the severity of the disease is age-dependent, but also dependent on the age of the onset of symptoms, and as such, quantifying each severity level in one simple description would not optimally estimate the true nature of the disease.

- **Inappropriate assumption regarding the future cost of asfotase alfa:** The manufacturer assumed that at year 10, loss of data exclusivity would lead to a 30% decrease in the list price of asfotase alfa (i.e., due to patent expiry and the availability of a generic entrant). There is substantial uncertainty associated with this assumption, given the likelihood for a manufacturer to produce a generic equivalent for a drug treating such a small patient population. Thus, at the present time, it is highly uncertain whether a generic alternative will be available in the future, when it might become available, and at what price.
- **Cost of wastage associated with treatment with asfotase alfa:** Asfotase alfa is dosed by patient weight and is available in pre-formulated strengths (18 mg, 28 mg, 40 mg in a 40 mg/mL vial and 80 mg in a 100 mg/mL vial) as single-use vials. In the model, the manufacturer assumed that the cost of treatment would be based on the per-milligram use, not accounting for wastage of partially used vials. This is inaccurate, given that public drug plans cover the cost of the entire vial and not per milligram used. The manufacturer stated in its response that it will be working with drug plans to contain costs and limit exposure to asfotase alfa wastage.

5. CADTH COMMON DRUG REVIEW REANALYSIS

CDR conducted several reanalysis scenarios that considered the key limitations identified. The following reanalyses were conducted:

1. Assuming the price of asfotase alfa will stay constant throughout the duration of the time horizon (no reduction in price). Upon changing this, the ICUR increased to $3,531,901 per QALY.
2. Assuming the costs associated with wastage are paid by the public payer. Upon changing this, the ICUR increased to $3,193,580 per QALY.

Upon conducting a multi-way analysis combining the two reanalyses above, the ICUR increased from $2,698,950 per QALY (calculated by CDR from manufacturer's results) to $4,080,555 per QALY.

3. Varying the utility weights using the lower and upper limits of the confidence intervals, which were calculated by multiplying the standard error by 1.96, as the confidence interval was not provided by the manufacturer. When assuming the upper limits, the ICUR increased from the CDR reference case ($4,080,555 per QALY) to $8,828,056 per QALY. When considering the lower limits, the ICUR was calculated to be $4,018,632 per QALY. The uncertainty regarding the derivation of the utility weights by the manufacturer has a substantial impact on the ICUR for asfotase alfa versus BSC.
4. Stratified analysis by patient severity level by assuming the proportion of patients in each health state at the onset of treatment (baseline) is 100%. Upon conducting this, based on the CDR reference case, when assuming all patients are in the least severe health state (severity level I), the ICUR was calculated to be $4,343,087 per QALY; when assuming all patients are in the severity level II health state, the ICUR was calculated to be $4,176,426 per QALY; when assuming all patients are in the severity level III health state, the ICUR was calculated to be $4,051,203 per QALY; and when

assuming all patients are in the severity level IV health state, the ICUR was calculated to be $3,616,563 per QALY.

5. Stratified analysis by patient age at the start of the model. Upon conducting this, based on the CDR reference case, when patients are treated at birth, this resulted in an ICUR of $2,276,483 per QALY; when patients are treated between the ages of zero and four years, the ICUR was calculated to be $2,675,263 per QALY; when patients are treated between the ages of five and 11 years, the ICUR was calculated to be $4,191,156 per QALY; when patients are treated between the ages of 12 and 17 years, the ICUR was calculated to be $5,160,860 per QALY; and when patients are treated after the age of 18 years, the ICUR was calculated to be $12,834,335 per QALY.

In a scenario in which all patients are in the most severe health state and start the model at birth, the ICUR was calculated to be $2,291,707 per QALY (based on the CDR reference case). As asfotase alfa appears to be most beneficial in patients who are in the most severe health state at the youngest age, driven by its impact on overall morbidity and mortality before the age of five, asfotase alfa is most cost-effective in this subpopulation.

A price reduction analysis was undertaken based on CDR's multi-way analysis estimate described above. This showed that even with a price reduction of 90%, the ICUR for asfotase alfa compared with BSC would still be higher than commonly accepted thresholds (Table 3).

TABLE 3: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Asfotase Alfa Versus Best Supportive Care		
Scenario (Price)	**Base-case analysis calculated by CDR based on manufacturer's results**	**Reanalysis by CDR[a]**
Submitted ($102.00)	$2,698,950	$4,080,555
10% reduction ($91.80)	$2,423,324	$3,666,768
20% reduction ($81.60)	$2,147,697	$3,252,981
30% reduction ($71.40)	$1,872,071	$2,839,195
40% reduction ($61.20)	$1,596,445	$2,425,408
50% reduction ($51.00)	$1,320,819	$2,011,621
60% reduction ($40.80)	$1,045,193	$1,597,835
70% reduction ($30.60)	$769,567	$1,184,048
80% reduction ($20.40)	$493,940	$770,261
90% reduction ($10.20)	$218,314	$356,475

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

[a] CDR reanalysis accounted for a constant price of asfotase alfa throughout the duration of the time horizon and included the costs associated with wastage of partially used vials.

6. ISSUES FOR CONSIDERATION

- HPP is a highly variable disease in terms of symptoms and clinical manifestations, at different ages. As such, the cost of care can be highly variable. The clinical expert noted that other costs not considered by the economic model may include psychologists; psychiatrists; pain medications; hearing-, audiology-, and ophthalmology-related care; and alternative treatments (e.g., bone marrow or stem cell therapies). All of these may incur additional costs to public drug plans.
- Genetic testing can be used to confirm the presence of HPP. As such, this would incur additional costs to public drug plans. However, considering the high price of the drug, and the relative low price for genetic testing (ranging from $250 to $870 per test),[11] and the important health benefit to be gained when the appropriate and optimal patient receives treatment, the use of genetic testing may increase the cost-effectiveness of the treatment. In study ENB-010-10, 24% of patients were misdiagnosed.[6]
- It should be noted that the clinical trials are limited by the small number of patients, upon which the clinical effectiveness in the model is based. Thus, the results of the clinical trials used to inform this economic evaluation are subject to a high degree of uncertainty.

7. PATIENT INPUT

Input was received from one patient group, Soft Bones Canada (SBC). In its submission, it was noted that the impact of HPP is often right from birth, and includes substantial pain and fatigue. Patients mentioned joint pain, muscular and bone pain, stiffness, and inflammation, all of which lead to physical and emotional exhaustion. Patients stated that there were no treatments for HPP prior to asfotase alfa, and that adjunctive therapies were used to help with the pain and fatigue aspects of living with HPP. The patients who have been on asfotase alfa described experiencing much less pain, improvement in physical ability, and overall improved quality of life. Patients noted that asfotase alfa was convenient and had minimal side effects. The manufacturer's model, which predicted the severity of the disease defined by the 6MWT outcome, may not have captured all important symptoms and manifestations of the disease, such as pain and fatigue, which may have undermined the benefit of the treatment from a cost-effectiveness perspective, especially when treating patients for whom optimal health benefits are expected.

8. CONCLUSIONS

Based on the manufacturer's submitted economic evaluation, CDR calculated the ICUR for asfotase alfa when compared with BSC to be approximately $2.7 million per QALY. CDR reanalysis addressing limitations regarding costs resulted in a significant increase to the ICUR to $4.08 million per QALY, which could be even higher given the substantial uncertainty associated with the model. Asfotase alfa appears to be most likely cost-effective in patients who are in a more severe health state and are treated at birth ($2.29 million per QALY).

APPENDIX 1: COST COMPARISON

Based on consultation with a clinical expert, no other drugs are currently indicated for this condition.

TABLE 4: COST COMPARISON TABLE FOR PEDIATRIC-ONSET HYPOPHOSPHATASIA

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose	Weekly Drug Cost ($)[b]	Annual Drug Cost ($)[b]
Asfotase alfa	18 mg 28 mg 40 mg	40 mg/mL single-use vial	$1,836.0000 $2,856.0000 $4,080.0000	2 mg/kg SC 3 times per week or 1 mg/kg SC 6 times per week	0-9 kg: $5,508[c] 10-14 kg: $8,568[d] 15-20 kg: $12,240[e] 21-40 kg: $24,480[f] 41-80 kg: $48,960[g]	$286,416 $445,536 $636,480 $1,272,960 $2,545,920
	80 mg	100 mg/mL single-use vial	$8,160.0000			

SC = subcutaneous.
[a] Manufacturer's submitted price, based on a price of $102.0000 per mg.[2]
[b] Assumes wastage covered by public payer.
[c] Assumes asfotase alfa is dosed at 2 mg/kg 3 times per week, where three 40 mg/mL vials of the 18 mg strength are used.
[d] Assumes asfotase alfa is dosed at 2 mg/kg 3 times per week, where three 40 mg/mL vials of the 28 mg strength are used.
[e] Assumes asfotase alfa is dosed at 2 mg/kg 3 times per week, where three 40 mg/mL vials of the 40 mg strength are used.
[f] Assumes asfotase alfa is dosed at 2 mg/kg 3 times per week, where three 100 mg/mL vials of the 80 mg strength are used.
[g] Assumes asfotase alfa is dosed at 1 mg/kg 6 times per week, where six 100 mg/mL vials of the 80 mg strength are used.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ASFOTASE ALFA RELATIVE TO THE BEST SUPPORTIVE CARE?

Asfotase Alfa vs. Best Supportive Care	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 cost-utility ratio	2.7 million per QALY (calculated by CDR based on manufacturer's results) 4.08 million per QALY (CDR reanalysis varying costs)					

CDR = CADTH Common Drug Review; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments *Reviewer to provide comments if checking "no"*	None		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 7: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review
☒ 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

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis based on a decision analytic Markov model where patients with a confirmed diagnosis of pediatric-onset hypophosphatasia (HPP) transition between four disease severity health states (I, II, III, and IV) based on the six-minute walk test (6MWT), in addition to a death health state (HPP-related and all-cause) and an invasive ventilator toll state (health state associated with a temporary disutility and costs).[2] In the manufacturer's base-case analysis, patients begin at the age of 5.8 years. The health states and the baseline distribution were defined as follows, based on 28 patients for whom there were 6MWT data available from studies ENB-006-09/ENB-008-10 and ENB-009-10:[4,5]

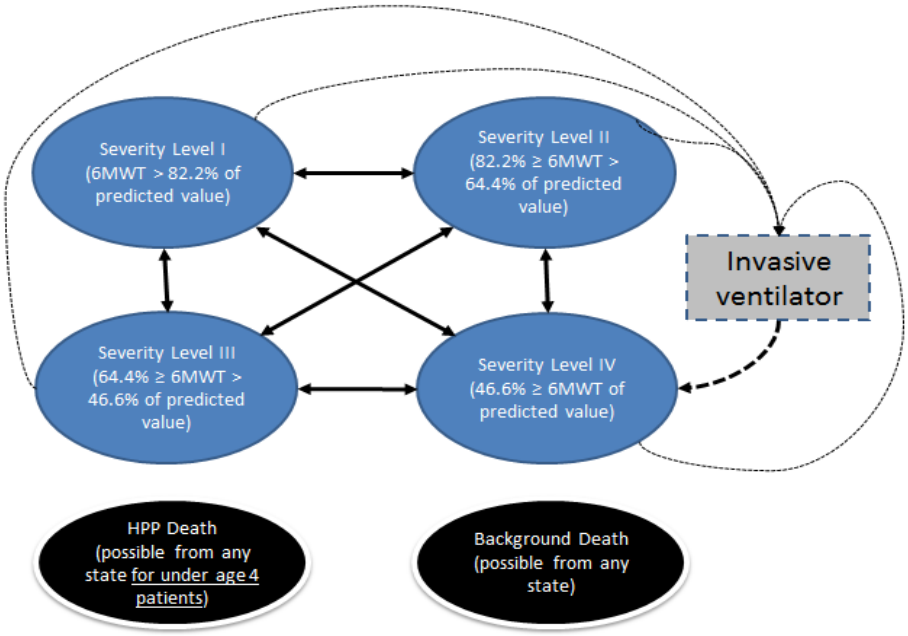
- Severity level I: (observed 6MWT/predicted 6MWT) > 82.2% (22.2 % of patients in this health state in the base-case)
- Severity level II: 82.2% ≥ (observed 6MWT/predicted 6MWT) > 64.4% (33.3% of patients)
- Severity level III: 64.4% ≥ (observed 6MWT/predicted 6MWT) > 46.6% (29.6% of patients)
- Severity level IV: (observed 6MWT/predicted 6MWT) > 46.6% or those who could not complete the 6MWT (14.8% of patients)
- HPP-related death: terminal health state based on HPP-related mortality (age-specific and occurred only in patients younger than five years)
- Background death: terminal health state based on mortality from causes other than HPP, based on age-specific rates in Canada
- Invasive ventilator toll state: toll state based on patients who required an invasive ventilator (age-specific and occurred only in patients younger than five years).

Note that the observed 6MWT results were based on trial observations and the predicted 6MWT was determined based on age, gender, and height-adjusted normative data (calculated and reported as per cent predicted distance walked in the trials), where a value of 100% would indicate a patient walked the expected distance based on their age, gender, and height. As there were no severity categories based on the 6MWT in HPP, the manufacturer used another disease to define each of the health states in this analysis. Specifically, the manufacturer considered Duchenne muscular dystrophy to be similar to HPP, where it was determined that the 6MWT was a reliable marker of disease severity. Using the minimal clinically important difference (MCID) reported in a published study in Duchenne muscular dystrophy patients, the manufacturer formed the basis for the thresholds between the four HPP severity health states.[2,9] It should be noted that there is no clear evidence to support this approach.

In the manufacturer's analysis, patients progressed through the health states every 12 weeks over a lifetime time horizon (assumed to be 101 years in the model).[2] Patients were able to transition to the mortality state (disease-specific and all-cause), or the invasive ventilator toll state from any of the severity states. In addition, if a patient was in the invasive ventilator toll state, they accrued a health utility decrement and additional medical costs, and further, they transitioned to the most severe health state (severity level IV). In the base-case analysis (where patients entered the model at 5.8 years old), the probability of being in the HPP-related death or invasive ventilator health state was 0%, as both of these outcomes were not observed past the age of four years in the trials. The manufacturer also conducted a scenario subgroup analysis based on varying the age at the start of the model (i.e., baseline age).[2]

Additionally, the manufacturer considered the severity of HPP to be age-dependent, where the risk of transitioning between severity states was based on clinical trial data, but included age as a covariate variable. As such, the manufacturer estimated an ordered probit regression model that allowed for the calculation of age-specific transition probabilities.[2]

FIGURE 1: MANUFACTURER'S PHARMACOECONOMIC MODEL



6MWT = six-minute walk test; HPP = hypophosphatasia.
Source: Manufacturer's pharmacoeconomic submission.[2]

The manufacturer stated that the technical aspects of the model were validated to ensure internal consistency. No external validity tests were performed.

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Natural History		
Historical control patients	• ENB-011-10, a retrospective natural history study in patients with severe perinatal or infantile-onset HPP, in patients aged ≤ 5 years.[7]	
Definition of health states	• Definition of health states was based on categorizing the per cent predicted distance walked by severity levels, using the MCID observed for the 6MWT outcome in a study conducted in patients with Duchenne muscular dystrophy study.[2,9]	
Mortality and invasive ventilator use	• HPP-related death and the need for invasive ventilator use was obtained from natural history study ENB-011-10.[7]	

Data Input	Description of Data Source	Comment
	• Background mortality was based on age-specific rates obtained from Statistics Canada life-tables.[2]	
Efficacy		
6MWT data	• 6MWT data were obtained from the following trials: ENB-006-09/ENB-008-10 (extension), a phase 2, open-label, randomized, historical control study in patients aged 5 to 12 years; and ENB-009-10, a phase 2, open-label, randomized, no-treatment concurrent control study in patients aged 13 to 65 years.[4,5]	6MWT was an exploratory or a secondary outcome in these studies. One treatment arm of ENB-006-09 and ENB-009-10 did not use the Health Canada–approved dosage of asfotase alfa. ENB-009-10 enrolled patients regardless of age of symptom onset (not necessarily pediatrics only).
Mortality and invasive ventilator use	• HPP-related mortality and invasive ventilator use were obtained from the following trials: ENB-002-08/ENB-003-08 (extension), a phase 2, open-label uncontrolled single-arm trial in patients aged ≤ 36 months; and ENB-010-10, a phase 2, open-label, uncontrolled single-arm trial, in patients aged ≤ 5 years.[3,12]	ENB-002-08/ENB-003-08 did not use the Health Canada–approved dosage of asfotase alfa.
Utilities	• Case histories were created for each health state based on two HPP natural history studies, ENB-011-10 and ALX-HPP-502, a retrospective, epidemiological study conducted in patients with juvenile-onset HPP (ages 5 to 15 years),[7,8] in addition to other published literature. Clinical experts then mapped these patient profiles to the 6MWT values and summarized them into descriptions of each health state, which were then used to rate using the EQ-5D-5L.	High degree of uncertainty associated with the manufacturer's approach of determining utility weights given the varied presentation of HPP.
Resource use	• Determined by estimating the frequency of clinical events expected in addition to the background care levels needed for each health state. This was refined and validated by a clinical expert.	Highly variable and uncertain due to the varied clinical symptoms and presentation of disease.
Costs		
Drug	• Manufacturer's submitted price	
Resources (cost per health state)	• The cost of each resource was obtained primarily from the Ontario Ministry of Health and Long-Term Care Schedule of Benefits for Physician Services (2015).[2] Other sources included published literature, manufacturer's websites, and other online sources.	

6MWT = six-minute walk test; EQ-5D-5L = EuroQol 5-Dimensions 5 Levels Questionnaire; HPP = hypophosphatasia; MCID = minimal clinically important difference.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The progression over time for asfotase alfa and BSC-treated patients can be derived from the trials using 6MWT data.	High degree of uncertainty. Not validated in patients with HPP.
The efficacy of treatment is maintained throughout the time horizon of the model.	High degree of uncertainty. Lack of long-term data to support this.
The Duchenne muscular dystrophy study can be used to identify severity levels in four health states that characterize HPP.	May be inappropriate. Adds to the uncertainty of the economic model results.
No excess risk of death for HPP patients after the last observed death in the trial, including those treated with asfotase alfa or BSC.	Appropriate assumption.
Patients in the invasive ventilator toll state transition to the severity level IV state.	Appropriate assumption.
Patients can move between any alive health states during a model cycle.	Appropriate assumption.
Patients who did not complete the 6MWT were in the severity level IV health state.	Appropriate assumption.
10 years from the start of the model, loss of data exclusivity leads to a 30% decrease in the price of asfotase alfa.	Not appropriate. Uncertain what the future cost of asfotase alfa will be.
Patients receive a combination of doses to minimize the number of patient injections on a daily and weekly basis.	Appropriate assumption.
Wastage occurs, but the public payer does not pay for these costs.	Not appropriate. The public payer will reimburse the cost of the entire vial.

6MWT = six-minute walk test; BSC = best supportive care; HPP = hypophosphatasia.

Manufacturer's Results

The manufacturer's base-case analysis results per patient over a lifetime time horizon are summarized in Table 10. Asfotase alfa was associated with a total cost of $28,338,582, which is an incremental cost of $27,728,012 versus best supportive care (BSC) ($610,570). Additionally, treatment with asfotase alfa resulted in 16.53 quality-adjusted life-years (QALYs), an incremental gain of 10.27 QALYs versus BSC (6.26 QALYs). The CADTH Common Drug Review (CDR) calculated that asfotase alfa versus BSC has an ICUR of $2,698,950 million per QALY.

TABLE 10: MANUFACTURER'S BASE-CASE ANALYSIS RESULTS, PER PATIENT

	Best Supportive Care	Asfotase Alfa	Incremental
Direct medical costs	$610,570	$21,767	–$588,803
Ventilation costs	$0	$0	$0
Drug costs	$0	$28,316,815	$28,316,815
Total costs	$610,570	$28,338,582	$27,728,012
Quality-adjusted life-years	6.26	16.53	10.27

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analysis

The manufacturer addressed uncertainty regarding the parameters chosen for the base-case analysis by conducting multi-way scenario analyses, one-way deterministic sensitivity analyses, and a probabilistic sensitivity analysis, with 500 iterations.

Scenario Analysis

The manufacturer conducted a scenario analysis in which it tested the model based on stratifying by patient age interval. This included the following subgroups: 1) patients diagnosed at birth; 2) patients aged zero to four years; 3) patients aged five to 11 years; 4) patients aged 12 to 17 years; and 5) patients aged 18 years and older. As shown in Table 11, the incremental benefit of treatment with asfotase alfa declines as the patient age at the start of the model increases, and as such, the ICUR also increases. Patients diagnosed at birth would benefit most with treatment with asfotase alfa.

TABLE 11: RESULTS OF SCENARIO ANALYSIS STRATIFYING BY PATIENT AGE INTERVAL

Patient Scenarios	Incremental Costs ($)	Incremental QALYs	ICUR
Base-case analysis[a]	27,728,012	10.3	$2,698,950
Diagnosed at birth (age 0)	19,357,755	13.3	$1,450,803
Trials age 0 to 4 (average age of 1.1 years)	20,940,971	12.2	$1,716,944
Trials age 5 to 11 (average age of 6.7 years)	28,877,228	10.3	$2,809,819
Trials age 12 to 17 (average age of 13.8 years)	36,836,501	9.5	$3,860,469
Trials age 18+ (average age of 51.6 years)	31,728,674	3.1	$10,369,516

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
[a] The base-case analysis uses an average age of patients in all of the trials (5.8 years old).
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

Deterministic Sensitivity Analysis

The parameters that were varied individually in each of the scenarios by the manufacturer were as follows:

- Utility values (mean ± 2 times the standard error)
- Costs of resources associated with each health state (± 20%)
- Ordered probit regression model specification used to determine age-specific transition probabilities (tested using specifications 1 and 3, which include different covariate variables)
- Efficacy of asfotase alfa, based on the 6MWT (ordered probit coefficients on lagged states increased and decreased by 2 times the standard error)
- Mortality rate (using predicted values)
- Threshold between the different severity levels (use of a lower [1×] and higher [3×] MCID value)
- Discount rate, for costs and utilities (0, 3.5%).

The following parameters had the greatest impact on the ICUR (± 25%): use of higher utility values; use of a different model specification; discount rate for costs and QALYs; and use of 3× the MCID value to determine thresholds for the severity states. When these parameters were varied individually, the ICUR for asfotase alfa versus BSC ranged from $635,820 to $11,727,390 per QALY.

Probabilistic Sensitivity Analysis

The variables considered in the probabilistic sensitivity analysis included baseline severity distribution; baseline age; utility values; utility decrement associated with ventilation; costs of resources associated with each health state; cost of ventilation and the ordered probit estimates (coefficients) for both BSC

and asfotase alfa. The manufacturer reported results of the probabilistic analysis in the form of histograms of the distribution for select variables.

CADTH Common Drug Review Reanalyses

CDR conducted several reanalyses based on the identified key limitations (i.e., utility weights, future cost of asfotase alfa, and the inclusion of drug costs accounting for wastage of partially used vials), in addition to a multi-way analysis. The time horizon was also tested to see how the results were affected.

The multi-way analysis, which varied only the limitations regarding the costs of asfotase alfa, resulted in an overall ICUR of $4,080,555 per QALY (Table 12).

TABLE 12: CADTH COMMON DRUG REVIEW REANALYSIS: ICURS FOR ASFOTASE ALFA VERSUS BSC

		ICUR (based on the manufacturer's base case)	ICUR (based on the CDR multi-way analysis that varied costs)[a]
Time horizon	5 years	$1,994,073	Not considered in multi-way analysis
	10 years	$2,468,012	
	20 years	$2,640,113	
	50 years	$2,693,179	
Utility weights	Mean + 1.96xSE	$5,839,030	
	Mean – 1.96xSE	$2,657,993	
Price of asfotase alfa is constant across the time horizon (i.e., no price reduction after 10 years)		$3,531,901	$4,080,555
Wastage paid by public payer		$3,193,580	
Stratification based on health state[b]	Severity level I	$2,874,192	$4,343,087
	Severity level II	$2,763,028	$4,176,426
	Severity level III	$2,679,357	$4,051,203
	Severity level IV	$2,389,070	$3,616,563
Stratification based on age at start of the model[c]	Birth (age 0)	$1,450,803	$2,276,483
	Age 0 to 4 years (average age of 1.1 years)	$1,716,944	$2,675,263
	Age 5 to 11 years (average age of 6.7 years)	$2,809,819	$4,191,156
	Age 12 to 17 years (average age of 13.8 years)	$3,860,469	$5,160,860
	Age 18+ years (average age of 51.6 years)	$10,369,516	$12,834,335

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; SE = standard error.
[a] Based on the parameters varied in the CDR multi-way analysis, including a constant price of asfotase alfa throughout the duration of the time horizon and including the costs associated with wastage of partially used vials.
[b] Assuming 100% of patients are in the respective health state.
[c] Note that stratification by age is limited by the sample size of patients in each age interval, and that more clinical data are needed to support this.

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