CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

ASFOTASE ALFA
(Strensiq — Alexion Pharma Canada Corp.)
Indication: Pediatric-onset Hypophosphatasia

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that asfotase alfa be listed for enzyme replacement therapy in patients with a confirmed diagnosis of pediatric-onset hypophosphatasia (HPP), if the following clinical criteria and conditions are met:

Clinical Criteria:
- Patient has infantile or childhood HPP confirmed by genetic testing.
- Patient is not an adult at the time treatment is initiated.

Conditions:
- Patients should be initiated on treatment and followed in a specialized clinic with expertise in the diagnosis and management of HPP.
- Goals of therapy should be developed on a case-by-case basis prior to the initiation of therapy. If these pre-specified goals are not met at reassessment following a trial of 24 weeks of therapy, the treatment should not be continued.
- Substantial reduction in price.

Reasons for Recommendation:
1. Three open-label pivotal studies (ENB-010-10 [N = 59], ENB-006-09 [N = 13], and ENB-008-10 [N = 12]) suggested that asfotase alfa 2 mg/kg administered three times per week is associated with an improvement in skeletal development.
2. Patients treated with asfotase alfa appeared to have a lower rate of mortality compared with the anticipated rate of mortality for patients with HPP, based on the natural history of this disease.
3. Reanalyses of the manufacturer's pharmacoeconomic model conducted by the CADTH Common Drug Review (CDR) suggested that the incremental cost-utility ratio (ICUR) for asfotase alfa can range from $4.02 million to $8.8 million per quality-adjusted life-year (QALY) compared with best supportive care (BSC). Therefore, asfotase alfa is not considered to be a cost-effective treatment option at the submitted price ($102.00 per mg).
4. Patient groups identified a substantial unmet need in the treatment of HPP that, CDEC concluded, could potentially be met by asfotase alfa.

Of Note:

- CDEC noted that for the purpose of determining the most appropriate patients over 12 years of age who could be treated with asfotase alfa, an adult should be defined as someone whose bone growth plates have closed.
- The clinical benefit of continuing treatment with asfotase alfa after closure of bone growth plates is uncertain.
- There are limited surrogate clinical data to support a clinical benefit of this agent in adults. In addition, the dosage of asfotase alfa is based on the weight of the patient; therefore, the cost of treatment is substantially greater for adults than for children and the cost-effectiveness of asfotase alfa is associated with a very high degree of uncertainty.
- Even with a price reduction of 90%, asfotase alfa is unlikely to be a cost-effective treatment option for HPP irrespective of the patient's age at treatment initiation.
- CDEC considered potential initiation and continuation criteria that were suggested by the clinical experts consulted during the CDR review and the committee's deliberations; however, there was no clinical or pharmacoeconomic evidence available to support the use of such criteria. In addition, the committee had concerns about the ability of the participating drug plans to operationalize the proposed clinical criteria in a heterogeneous patient population, many of whom would be infants and young children. CDEC noted that the CDR-participating drug plans and the HPP clinical expert community need to establish case-by-case evaluation criteria for the initiation and continuation of asfotase alfa.
- There were no patients in the pivotal studies who were older than 12 years. However, CDEC noted that there were a number of children with HPP who were older than 12 years at the time this recommendation was made. These children could potentially benefit from treatment with asfotase alfa.

Background:

Asfotase alfa is a therapeutic protein intended to act in place of the defective endogenous tissue non-specific alkaline phosphatase enzyme. It is indicated for use as enzyme replacement therapy for patients with confirmed HPP. The recommended dose is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials and pivotal studies of asfotase alfa, a critique of the manufacturer's pharmacoeconomic evaluation, and information submitted by patient groups about outcomes and issues that are important to individuals living with HPP.

Patient Input Information

One patient group, Soft Bones Canada, responded to the CDR call for patient input. Information was obtained from patients and caregivers through one-to-one conversations by telephone and email, and by meeting with families. The following is a summary of key information provided by the patient group:

- HPP begins affecting many patients in infancy, and its two constants are pain and fatigue. The chronic joint pain associated with HPP severely affects patients' quality of life and mobility. In addition, the pain can cause patients to suffer from overwhelming frustration, mental fog, impatience with family members, anxiety, fear, depression, and a lack of intimacy. Fatigue associated with HPP can cause children to miss school and adults to miss

work. It can have a profoundly negative impact on the ability of patients to participate in social, family, and leisure activities.
- Children with HPP can experience craniosynostosis, stress fractures in the legs and hips, poor appetite and slow growth, stomach pains, frequent vomiting, and abnormal development of teeth. Adults with HPP commonly experience severe dental problems, difficulties with balance and sleep, fractures that are slow to heal, and nerve damage.
- HPP thoroughly and permanently alters the lives of caregivers, who often experience significant financial and emotional strain when caring for a loved one with this condition.
- Patients and caregivers noted that asfotase alfa is the first therapy approved for use in the treatment of HPP and they hope it can both extend the lives of patients and improve their quality of life. They indicated that they would be willing to accept extensive side effects if treatment with asfotase alfa could improve their overall quality of life. Parents of children who have been treated with asfotase alfa and adult patients who have been treated with asfotase alfa have reported considerable benefits and no serious adverse events.

Clinical Trials

Three clinical trials identified by Health Canada as pivotal were included in the CDR systematic review:
- ENB 010-10 (N = 59) was a phase 2, open-label, single-arm trial conducted in patients aged five years or younger with infantile HPP. Patients received a dose of 2 mg/kg three times per week or 1 mg/kg six times per week.
- ENB-006-09 (N = 13) was a phase 2, open-label, randomized, historically controlled, dose-ranging study conducted in patients aged between five and 12 years, with no specific requirement regarding the time of diagnosis of HPP. Patients were randomized to receive either 2 mg/kg three times per week (6 mg/kg/week) or 3 mg/kg three times per week (9 mg/kg/week).
- ENB-008-10 (N = 12) is the single-arm extension study of ENB-006-09. Patients were initially administered a total of 3 mg/kg/week; however, this was later increased to a total dose of 6 mg/kg/week.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:
- Mortality.
- Radiographic Global Impression of Change (RGI-C) — a scale designed by the manufacturer to measure the change in the severity of rickets (i.e., the softening and weakening of bones in children). RGI-C is a seven-point change scale that provides an assessment of the change in bone structure associated with the pathophysiology of HPP. A reduction of three points represents severe worsening and an increase of three points indicates complete healing of the skeletal disease.
- Rickets severity scale (RSS) — a 10-point scale (four points for the wrists and six points for the knees) used to evaluate the severity of rickets. Assessment of the wrists and knees is based on the degree of metaphyseal fraying and cupping and the proportion of growth plate affected. A score of 10 represents severe rickets, while a score of 0 indicates an absence of metaphyseal cupping and fraying.
- The six-minute walk test (6MWT) — a test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.

- Serious adverse events, total adverse events, and withdrawals due to adverse events.

RGI-C measured at 24 weeks was the primary outcome in the included studies.

Efficacy

- In ENB-006-09, patients treated with asfotase alfa demonstrated a statistically significant improvement in RGI-C score compared with the historical control group [redacted]. The median RGI-C at 24 weeks was [redacted] in the asfotase alfa group and [redacted] in the historical control group. The improvement in RGI-C observed during the core study (ENB-006-09) was maintained in the extension study (ENB-008-10). In ENB-010-10, there was a statistically significant improvement in RGI-C from baseline, with a median of [redacted].
- In ENB-006-09, the asfotase alfa treatment group demonstrated improvement in median RSS at 24 weeks [redacted] compared with the historical control group [redacted]. In the uncontrolled studies, the median change from the baseline was [redacted] in ENB-010-10 and [redacted] in ENB-008-10.
- In ENB-008-10, patients at baseline were able to walk a median of [redacted] of the predicted distance. The median change from baseline in the 6MWT was [redacted] at 24 weeks and [redacted] at 240 weeks.
- In ENB-008-10, patients treated with asfotase alfa demonstrated an increase in whole body bone mineral content; the median increase was [redacted] at 24 weeks [redacted] at 264 weeks.
- Evidence from the included studies, as well as additional clinical evidence, suggested that patients with infantile HPP who were treated with asfotase alfa had a lower mortality rate than what has been observed in the natural history of the disease.

Harms (Safety and Tolerability)

- Adverse events in asfotase alfa–treated patients were primarily related to the subcutaneous route of administration. Across all studies, injection- and infusion-related adverse events (e.g., injection site redness, tenderness, and pain) constituted the majority of adverse events.

[redacted]

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing asfotase alfa to BSC (defined as the use of surgical interventions, hospitalizations, intensive care unit services, respiratory assistance, outpatient visits, consultations, and pain medication, as needed) in patients with a confirmed diagnosis of pediatric-onset HPP. The model was based on a lifetime time horizon (up to 101 years) and was conducted from the perspective of the Canadian publicly funded health care system.

The model consisted of six health states, four of which were defined by the severity level of disease, based on an observed or predicted 6MWT score. Other health states included death due to HPP and background death, in addition to an invasive ventilator toll state (i.e., a

temporary health state associated with disutility and additional costs). The manufacturer's analysis used data from four clinical trials (ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, and ENB-010-10) and two natural history studies (ENB-011-10 and ALX-HPP-502). The manufacturer considered the severity of HPP to be age-dependent, and as such, calculated age-specific transition probabilities, using predictive modelling where data were not available. Additionally, the manufacturer conducted a utility elicitation study to determine utility weights for each of the health states. The manufacturer did not report a base-case ICUR; rather, results disaggregated by costs and benefits were reported. CDR calculated an ICUR of $2,698,950 per QALY based on the manufacturer's results.

CDR identified a number of limitations with the manufacturer's submission:

- 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 assessed or validated 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 that the loss of market exclusivity in 10 years would lead to a 30% decrease in the future price of asfotase alfa
- Inappropriate assumption that no costs would be associated with the wastage of partially used vials of asfotase alfa.

CDR reanalysis addressing the two limitations regarding the costs of asfotase alfa resulted in an ICUR of $4.08 million per QALY versus BSC; even higher ICURs are possible, given the substantial uncertainty associated with the model. Additionally, treatment with asfotase alfa is more cost-effective in patients who have a higher severity of disease and are treated at an earlier age (using the CDR reference case, the ICUR was calculated to be $2.29 million per QALY for patients in the most severe health state treated at birth).

Asfotase alfa is priced at $102/mg. At the recommended dose of 2 mg/kg of body weight three times per week or 1 mg/kg of body weight six times per week, the annual cost will exceed $1 million for patients weighing more than 20 kg.

Genetic testing can be used to confirm the presence of HPP. Considering the high price of the drug, and the relatively low price for genetic testing (ranging from $250 to $870 per test), the use of genetic testing is likely to increase the cost-effectiveness of the treatment by avoiding treatment of misdiagnosed patients.

Other Discussion Points:
CDEC noted the following:

- There are no Canadian guidelines available on discontinuation of treatment with asfotase alfa.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- The safety and efficacy of asfotase alfa have not been evaluated in controlled clinical trials.
- As a condition of market authorization, the manufacturer has agreed to provide Health Canada with safety and efficacy data for HPP patients aged 13 to 18 years.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

January 20, 2016 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has/has not requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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