



Australian Government

Department of Health

# Life Saving Drugs Program – Asfotase alfa (Strensiq®) outcome statement



# Summary of the consideration of the application from Alexion Pharmaceuticals Australasia Pty Ltd for the inclusion of asfotase alfa (Strensiq®) on the Life Saving Drugs Program (LSDP) for the treatment of perinatal- and infantile-onset hypophosphatasia (HPP)

## Overview:

The LSDP Expert Panel (the Panel) advises the Chief Medical Officer (CMO) on new medicine applications to the LSDP. Asfotase alfa was considered for listing on the LSDP at the Expert Panel's meeting on 10 October 2021.

## Background:

Asfotase alfa is an enzyme-replacement therapy (ERT) approved by the Therapeutic Goods Administration (TGA) for use in patients with HPP. HPP is an ultra-rare disease, characterised by defective bone mineralisation and impaired phosphorus and calcium regulation. It is caused by gene mutations in the *ALPL* gene, which codes for the tissue non specific alkaline phosphatase (ALP) enzyme. Patients with HPP are deficient in or lack the ALP enzyme and as a result phosphate and calcium cannot bind together properly to form healthy mineralised bones, resulting in chest wall instability and respiratory complications and additional rickets-like deformities. Rib deformities and fractures predispose infants to pneumonia and can progress to life-threatening respiratory failure.

Neurotransmitter synthesis in the brain is also compromised, resulting in vitamin B6-dependent seizures. Often, babies with disease onset before or at birth (perinatal-onset HPP) have the most severe form of HPP which is almost always fatal. Mortality in infantile-onset (0-6 months) HPP is estimated to be 50% in the first year of life. Premature death is primarily due to respiratory failure related to hypo-mineralisation of the ribs, thoracic instability, fractures and muscle weakness.

## Pharmaceutical Benefits Advisory Committee (PBAC)

### Consideration:

At its July 2017 meeting, PBAC considered a submission from Alexion requesting the listing of asfotase alfa on the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with HPP. PBAC did not recommend the listing of asfotase alfa. PBAC considered that asfotase alfa was not cost-effective in the perinatal- and infantile-onset population at the proposed price. PBAC advised that the persistence of survival gains with asfotase alfa in this severe patient group beyond five years is uncertain and further evidence would be required to support ongoing use beyond five years of age in this population. Further information on PBAC's consideration of asfotase alfa including reasons for rejection is available in the PBAC Public Summary Document: <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2017-07/asfotase-alfa-rch-psd-july-2017>

### Consumer Input:

The Panel noted the consumer input from PBAC and the LSDP applications. The Panel found the insight provided by the stakeholders was informative and contributed to its deliberations.

## LSDP Expert Panel Consideration:

### Funding Criteria

In order to be included in the LSDP, a medicine must be considered to meet each of the LSDP funding criteria A1-A8. A summary of the claims for asfotase alfa against each criterion is presented below.

LSDP criteria		How asfotase alfa meets the criteria
<b>A1</b>	<b>There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration (prevalence of <math>\leq 1</math> per 50,000 people).</b>	Asfotase alfa was designated as an orphan drug by the TGA in 2012 and has been listed on the ARTG since 2016 as an enzyme replacement therapy in patients with paediatric-onset HPP, with the eligible population for LSDP listing reflecting a subpopulation of the approved indication (those with perinatal- or infantile-onset HPP). The estimated birth prevalence of perinatal- and infantile-onset HPP is 1 per 297,000 (or 3.4 per 1,000,000) live births.
<b>A2</b>	<b>The disease is identifiable with reasonable diagnostic precision</b>	A blood test showing ALP levels below the normal range for the patient's age and sex is usually sufficient to confirm HPP (MBS funded; item 66512). Diagnosis is also based on family background, symptoms and results of radiographic imaging. Deformities are usually visible at birth and rapidly result in breathing difficulties. An X-ray will show significant lack of bone mineralisation.  In case of doubt (following a low ALP reading), elevated serum pyridoxal 5'-phosphate (PLP) or urine phosphoethanolamine (PEA) or genetic testing can also be used to confirm diagnosis.
<b>A3</b>	<b>Epidemiological and other studies provide evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease</b>	In perinatal and infantile forms of HPP, the literature notes the 1-year mortality rate of 100% for perinatal-onset HPP and 50% for infantile-onset HPP, primarily due to respiratory failure related to hypo-mineralisation of the ribs, thoracic instability, and muscle weakness. A retrospective chart review (study ENB-011-10) describing the natural history of perinatal- and infantile-onset HPP at high risk of premature death and receiving best supportive care, confirmed the high rate of mortality: 5-year overall survival of these patients is 27%.
<b>A4</b>	<b>There is evidence to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug</b>	Pooled survival analyses from asfotase alfa studies ENB-002-08/002-09 and ENB-010-10 in patients with perinatal- or infantile-onset HPP at high risk of premature death demonstrate that treatment with asfotase alfa significantly extends a patient's lifespan compared with historical controls receiving best supportive care (study ENB-011-10). The probability of survival at 7 years for treated patients was 87% (95% CI: 0.77, 0.93) versus 27% (95% CI: 0.15, 0.40) for historical controls receiving best supportive care (Högler et al. 2019).  The asfotase alfa studies also demonstrate improvement in physical function, ambulation, disability and quality of life.

LSDP criteria		How asfotase alfa meets the criteria
A5	<b>The drug must be accepted as clinically effective but rejected for PBS listing because it fails to meet the required cost effectiveness criteria.</b>	<p>In 2017 PBAC accepted that there is likely to be a survival benefit associated with treatment with asfotase alfa for children with perinatal- or infantile-onset (i.e. up to 6 months of age) HPP who were at high risk of premature death.</p> <p>PBAC also concluded that <i>“asfotase alfa is not cost-effective in the perinatal- and infantile-onset population at the proposed price”</i>. The updated model based on the proposed reduced price resulted in an ICER of &gt; \$1,055,000 confirming that asfotase alfa remains suitable for inclusion on the LSDP for the proposed populations.</p>
A6	<p><b>There is no alternative drug listed on the PBS or available for public hospital in-patients which can be used as lifesaving treatment for the disease.</b></p> <p><b>However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for inclusion on the LSDP.</b></p>	<p>There is no alternative drug listed on the PBS, LSDP or available for public hospital in-patients which can be used as a life-saving therapy for patients with perinatal- or infantile-onset HPP at high risk of death.</p> <p>Any available drug therapy used as part of best supportive care (BSC) merely control or manage the many symptoms and complications of the disease, rather than treat the underlying condition itself. BSC drug management options may include anticonvulsants, analgesics, antibiotics and/or corticosteroids, loop diuretics and calcitonin administration. Given none of these interventions address the underlying aetiology of the disease, they are unable to modify the course or the progression of disease. To this end, there is a high unmet clinical need for an effective and safe treatment to be listed on the LSDP for the proposed population.</p>
A7	<b>There is no alternative non-drug therapeutic modality (eg surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost-effective treatment for this condition.</b>	<p>There is no alternative non-drug therapeutic modality which is recognised by medical authorities as a suitable and cost-effective treatment for this condition.</p> <p>BSC focuses on controlling or managing the many symptoms and complications of the disease, including supporting vital functions such as respiration, managing seizures, nutritional status and renal function. For surviving infants, other supportive care may include surgical interventions, dietary modification, physiotherapy/occupational therapy and/or dental care. Procedures such as surgery or mechanical ventilation do not prevent or delay disease progression, and most patients continue to experience significant morbidity or risk of mortality.</p>
A8	<b>The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one-year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.</b>	<p>The TGA recommended dosage regimen is 2 mg/kg of body weight, administered subcutaneously 3 times per week, or 1 mg/kg of body weight administered 6 times per week.</p> <p>At the proposed asfotase alfa price of \$[REDACTED] per mg, the annual per patient treatment cost would be \$[REDACTED] for a 10 kg infant, representing an unreasonable financial burden on the patient or guardian.</p>

## Pricing issues

During assessment, it was noted that the proposed cost of asfotase alfa was high relative to the cost of other LSDP funded ERTs.

Note that the price of all LSDP medicines are subject to commercial in confidence arrangements.

## Treatment Guidelines:

The application included draft Guidelines for the treatment of HPP through the LSDP, which proposed initial and ongoing eligibility requirements. The Guidelines proposed that:

- The diagnosis of HPP must have been confirmed by the following:
  - ALP activity below the lower limit of normal (age- and sex adjusted).
  - Exclusion of non-HPP-related causes of low ALP activity OR confirmation of HPP via PLP AND/OR urine PEA AND/OR genetic testing.
  - Paediatric medical records documenting HPP-related symptoms.
  - History of HPP-related bone disease, as assessed by skeletal imaging (radiography).
- The patient must satisfy the following criteria to be eligible for treatment with asfotase alfa:
  - perinatal- or infantile-onset HPP in patients at time of the initial LSDP application, with a history of any of the disease manifestations listed below:
    - Respiratory compromise requiring ventilatory support OR
    - Vitamin B6-dependent seizures OR
    - Rachitic chest deformity.

## Management of Uncertainties

To address uncertainties, clinical data will be collected through initial and ongoing applications to the LSDP. In line with LSDP policy and to manage uncertainties, a review of asfotase alfa 24 months after listing would be conducted to ensure use and performance of the medicine is in line with the expectations at the time of listing.

## Context:

The LSDP provides access for eligible patients with rare and life-threatening diseases to essential and very expensive medicines. The LSDP provides eligible patients with access to these life-saving medicines at no expense to the patients or their families.

Before being considered for inclusion on the LSDP, a drug must first be considered by PBAC and accepted as clinically effective but rejected for PBS listing because it fails to meet the required cost effectiveness criteria.

All applications for new medicines seeking funding through the LSDP are considered by the LSDP Expert Panel. The role of the panel is to provide advice and assistance to the CMO on a range of matters relating to new medicines seeking funding, including assessment of how the medicine addresses the LSDP criteria, guidelines for medicine use and testing requirements, suitable pricing arrangements, and data collection required for future reviews.

After receiving advice from the Panel, the CMO advises the Minister for Health on medicines proposed to be included on the LSDP.

This document aims to provide an overview of the evidence considered by the Panel and CMO during their assessment of medicines.

For more information on the process for new medicines seeking funding through the LSDP, refer to the LSDP Procedure guidance: <https://www.health.gov.au/resources/publications/procedure-guidance-for-medicines-funded-through-the-life-saving-drugs-program-lsdp>

## Sponsor's Comment:

*Alexion welcomes the listing of asfotase alfa (Strensiq®) for Australian children diagnosed with perinatal- or infantile-onset HPP on the Life Saving Drugs Program.*