## Pharmacotherapy of Perinatal/Infantile and Juvenile-Onset Hypophosphatasia (HPP)

<table>
<thead>
<tr>
<th>Effective Date:</th>
<th>June 1, 2023</th>
<th>RELATED MEDICAL POLICIES:</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Revised:</td>
<td>May 22, 2023</td>
<td></td>
<td></td>
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<tr>
<td>Replaces:</td>
<td>N/A</td>
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### Introduction

Hypophosphatasia (HPP), also known as phoshoethanolaminuria, Rathbun disease, or HOPS, is a rare metabolic bone disease. It is caused by mutations in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP) that fail to activate. TNSALP is an enzyme that plays a large role in the body’s process of building minerals on the structure of the bone. There are different forms of HPP based on the age of onset: perinatal/infantile (before 6 months of age), juvenile, and adult. The severe forms of HPP only occur in about 1:100,000 births in the U.S., but in the Canadian Mennonite population, 1:2500 infants die from this disease.

A drug called Strensiq® (asfotase alfa) is approved to treat HPP. There were no drugs available before that were effective to treat HPP. This policy outlines when Strensiq® may be covered.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

### Policy Coverage Criteria

5.01.573_PBC (05-22-2023)
### Drug Medical Necessity

**Strensiq® (asfotase alfa)**

*Strensiq® (asfotase alfa) may be considered medically necessary for the treatment of individuals with genetically confirmed perinatal/infantile- and juvenile-onset hypophosphatasia (HPP) when:*

- The onset of the disease is perinatal/infantile or juvenile (≤ 18 years of age)
  
AND

- Genetic testing showing mutation status of the ALPL protein (gene encoding alkaline phosphatase)
  
AND

- Blood test showing age adjusted serum levels of alkaline phosphatase (ALP) below the lower limit of normal at time of diagnosis
  
AND

- Plasma pyridoxal 5’-phosphate (PLP) levels are greater than the upper limit of normal at time of diagnosis
  
OR

- Urinary phosphoethanolamine (PEA) are greater than the upper limit of normal at time of diagnosis
  
AND

- Skeletal radiographs at time of diagnosis supports HPP (eg, bone deformities, osteomalacia, calcific periarthritis, or atypical fractures)

### Drug Investigational

**Strensiq® (asfotase alfa)**

*All other uses of Strensiq® (asfotase alfa) are considered investigational including use for adult-onset hypophosphatasia (HPP).*

### Length of Approval

<table>
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<tr>
<th>Approval</th>
<th>Criteria</th>
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<tr>
<td>Initial authorization</td>
<td>Strensiq® (asfotase alfa) may be approved up to 6 months.</td>
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<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of Strensiq® (asfotase alfa) may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the</td>
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Length of Approval

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<tr>
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<th>Criteria</th>
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<tbody>
<tr>
<td></td>
<td>individual continues to show a positive clinical response to therapy as supported by skeletal radiographs, ALP, PEP and/or PEA levels.</td>
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</table>

Documentation Requirements

The individual’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, genetic and lab tests results, skeletal radiographs, and the individual’s medical history documenting infantile or juvenile onset.

Coding

N/A

Related Information

Benefit Application

This policy is managed through the Pharmacy benefit.

Consideration of Age

The age noted in the policy statement (perinatal/infantile, juvenile-onset) is based on the FDA labeling for this agent.

Evidence Review
Disease Background

Hypophosphatasia (HPP) is caused by deficiency of tissue-nonspecific alkaline phosphatase (TNSALP) activity. This loss of function is associated with accumulation of substrates such as inorganic pyrophosphate (PPi) and pyridoxyl 5'-phosphate (PLP), the main circulating form of vitamin B6. PPi blocks hydroxyapatite crystal growth which inhibits bone mineralization and causes an accumulation of unmineralized bone matrix that manifests as rickets and bone deformation in infants and children and as osteomalacia (softening of bones) once growth plates close, along with muscle weakness.

The clinical manifestations of HPP are primarily skeletal, including rickets, osteomalacia, fractures, and deformities. Abnormalities of the thoracic cage can result in respiratory complication. Nonskeletal manifestations include pyridoxine-responsive seizures (in absence of TNSALP, pyridoxal 5'-phosphate cannot cross the blood-brain barrier), hypercalcemia, hypercalciuria (including nephrocalcinosis), myopathy (which can contribute to delayed or abnormal gait), and dental manifestations.

Severity of the disease varies from stillbirth or death during the neonatal period to clinical forms that have mostly dental manifestations or minimal bone findings. Usually, the severity of HPP is inversely related to age, with the neonatal form being the most severe. Historically, mortality in the severe perinatal/infantile subtype has ranged from 50-100% in the first year of life, primarily due to respiratory complications.

Strensiq® (asfotase alfa)

Strensiq® (asfotase alfa) is a targeted enzyme replacement therapy produced by recombinant DNA technology for the treatment of infantile- and juvenile-onset HPP. HPP is a rare and often severe and life-threatening condition caused by inherited genetic mutations in the gene encoding TNSALP. Four fair quality studies provide evidence of efficacy and safety. Although the study designs and sample sizes of these trials were not ideal, they are considered adequate evidence of efficacy and safety given the rarity of the condition, the consistency in findings of clinically relevant improvements compared to historical controls, and because there is no other disease-modifying treatment alternative available. All forms of hypophosphatasia (except pseudohypophosphatasia) share in common reduced activity of unfractionated serum alkaline phosphatase (ALP) and presence of either one or two pathogenic variants in ALPL, the gene
encoding alkaline phosphatase, tissue-nonspecific isozyme (TNSALP). Genetic testing should be used to confirm the diagnosis.

In 99 individuals with perinatal/infantile- or juvenile-onset HPP ages 1 day to 58 years treated with asfotase alfa more than 2 years, the most common AE was injection site reactions (63%). These events occurred at a greater frequency in the juvenile-onset cohort than in the perinatal/infantile-onset cohort. Other common AEs (occurring in ≥10% of individuals from the registration studies) were lipodystrophy (28%), ectopic calcifications (14%), and hypersensitivity reactions (12%).

**Evidence of Efficacy**

There are eight fair quality phase II, multicenter, open-label, cohort studies comprising the evidence of efficacy and safety for asfotase alfa in individuals with HPP. Five of these studies demonstrate long-term efficacy to at least 5 years post-initiation. While the study designs and sample sizes of these trials was not ideal, they are considered adequate evidence of efficacy given the rarity of the condition and consistency in disease manifestation improvements compared to historical controls.

**Evidence of Safety**

In individuals with perinatal/infantile- or juvenile-onset HPP treated with AA for up to 5 years, the most common AEs were injection site reactions (63%), lipodystrophy (28%), ectopic calcifications (14%), and hypersensitivity reactions (12%). Additionally, a majority (75%) individuals tested positive for anti-AA antibodies at some time during study and about half of these individuals also developed neutralizing antibodies. However, the only clinical effect identified was a reduced systemic exposure.

**2018 Update**

A literature search from 1/1/2017 through 2/28/2018 did not identify new information requiring change to the medical policy criteria. Added duration of authorization, reauthorization criteria, documentation requirements, and removed the Dosage and Quantity Limit table.
2019 Update

A literature search from 1/1/2018 through 3/31/2019 did not identify new information requiring change to the medical policy criteria.

2020 Update

A literature search from 3/1/2019 through 8/31/2020 did not identify new information requiring change to the medical policy criteria. Updated Evidence of Efficacy section to include additional clinical trials that have been published.

2021 Update

Reviewed Strensiq® (asfotase alfa) prescribing information and conducted a literature search on the management of hypophosphatasia. No new information was identified that would result in changes to policy statements.

2022 Update

Reviewed Strensiq® (asfotase alfa) prescribing information and conducted a literature search on the management of hypophosphatasia from 8/31/2020 through October 19, 2022. No new information was identified that would result in changes to policy statements.

2023 Update

Reviewed Strensiq® (asfotase alfa) prescribing information. No new information was identified that would result in changes to policy statements.

References

### History

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<th>Comments</th>
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<tbody>
<tr>
<td>04/01/17</td>
<td>New policy, approved March 14, 2017. Add to Prescription Drug section. Asfotase alfa (Strensiq®) may be considered medically necessary to treat infantile- and juvenile-onset HPP when criteria are met. All other uses are considered investigational. Reviewed and approved by P&amp;T Committee, February 2017.</td>
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<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Added duration of authorization, reauthorization criteria and documentation requirements. Removed Dosage and Quantity Limit table.</td>
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<tr>
<td>09/21/18</td>
<td>Minor update. Added Consideration of Age statement.</td>
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<tr>
<td>05/01/19</td>
<td>Annual Review, approved April 18, 2019. No change to policy statement. Removed HCPCS code J3490, added J3590.</td>
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<tr>
<td>09/01/19</td>
<td>Interim Review, approved August 13, 2019. Updated Strensiq criteria and added additional criteria that support the diagnosis of hypophosphatasia. Removed HCPCS code J3590.</td>
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<td>10/01/20</td>
<td>Annual Review, approved September 17, 2020. No change to policy statement.</td>
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<td>01/01/22</td>
<td>Annual Review, approved December 2, 2021. No changes to policy statements.</td>
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<tr>
<td>12/01/22</td>
<td>Annual Review, approved November 7, 2022. No changes to policy statements. Changed the wording from &quot;patient&quot; to &quot;individual&quot; throughout the policy for standardization.</td>
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<tr>
<td>06/01/23</td>
<td>Annual Review, approved May 22, 2023. No changes to policy statements.</td>
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