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 Strepsiq® (asfotase alfa) was recently approved to treat HPP. There were no drugs available before that were effective to treat HPP. This policy outlines when Strepsiq® 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

## Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strensiq® (asfotase alfa)</td>
<td>Strensiq® (asfotase alfa) may be considered medically necessary for the treatment of patients with genetically confirmed perinatal/infantile, and juvenile-onset hypophosphatasia (HPP).</td>
</tr>
</tbody>
</table>

Initial approval for six months requires all of the following:
- Genetic* AND lab testing** have been used to confirm the diagnosis and reports provided with prior authorization request

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

**Lab testing
- Blood test showing serum levels of the Alkaline Phosphatase (ALP)

All other uses of asfotase alfa and for conditions not outlined in this policy are considered investigational.

## Reauthorization

Continued therapy will be approved for periods of three years as long as the above conditions are met, and the patient has shown and continues to show benefit from the treatment.

## Required Documentation

- Initial approval requires chart notes including lab test reports documenting the above diagnostic testing, patient history documenting infantile or juvenile onset.
- Reauthorization requires chart notes showing current ALP levels and evidence

## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>J3490</td>
<td></td>
</tr>
</tbody>
</table>
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 B$_6$. 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.

**Streksiq® (asfotase alfa)**

Streksiq® (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. Treatment cost is estimated at $285,000/patient/year; however, value remains to be established. Since it was approved, utilization data show some adult patients have received it that do not appear to have hypophosphatasia. 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 patients 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 patients from the registration studies) were lipodystrophy (28%), ectopic calcifications (14%), and hypersensitivity reactions (12%).

**Evidence of Efficacy**

There are four fair quality phase II, multicenter, open-label, cohort studies comprising the evidence of efficacy and safety for asfotase alfa in patients with HPP. 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 patients 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%) patients tested positive for anti-AA antibodies at some time during study and about half of these patients 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.

References

2. Data on file, Alexion Pharmaceuticals; ENB-002-08/ENB-003-08


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<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>
</tr>
<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>
</tr>
<tr>
<td>09/21/18</td>
<td>Minor update. Added Consideration of Age statement.</td>
</tr>
</tbody>
</table>

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**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

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PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

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Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impormasion maipanggepp iti aplikasyon yo yonfery coverager babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pesa iti daytoy a pakdaar. Mabalini nga adda rumbung a ariyendi nga addag sakyb dagiti partikul ariyendi nga adda taidan tapo mapagtalaineyo ti coverager ti salan-ayyo yonfery tajuk dagaityo gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tajuk ti bukodyo a pagasaa nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

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