**PHARMACY POLICY – 5.01.573**

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

<table>
<thead>
<tr>
<th>Effective Date:</th>
<th>April 1, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Revised:</td>
<td>Mar. 14, 2017</td>
</tr>
<tr>
<td>Replaces:</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**RELATED MEDICAL POLICIES:** None

---

Select a hyperlink below to be directed to that section.

- **POLICY CRITERIA**
- **CODING**
- **RELATED INFORMATION**
- **EVIDENCE REVIEW**
- **REFERENCES**
- **HISTORY**

∞ Clicking this icon returns you to the hyperlinks menu above.

---

**Introduction**

Hypophosphatasia (HPP), also known as phosphoethanolaminuria, 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 asfotase alfa (Strensiq®) was recently 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asfotase alfa (Strensiq®)</td>
<td>Asfotase alfa may be considered medically necessary for the treatment of patients with perinatal/infantile, and juvenile-onset hypophosphatasia (HPP) when:</td>
</tr>
<tr>
<td></td>
<td>• Genetic* AND lab testing** have been used to confirm the diagnosis and reports provided with prior authorization request</td>
</tr>
<tr>
<td></td>
<td>*Genetic testing</td>
</tr>
<tr>
<td></td>
<td>• Gene testing showing mutation status of the ALPL protein (gene encoding alkaline phosphatase)</td>
</tr>
<tr>
<td></td>
<td>**Lab testing</td>
</tr>
<tr>
<td></td>
<td>• Blood test showing serum levels of the Alkaline Phosphatase (ALP)</td>
</tr>
<tr>
<td></td>
<td>All other uses of asfotase alfa and for conditions not outlined in this policy are considered investigational.</td>
</tr>
<tr>
<td></td>
<td>Note: Recommended dosing can be found in the Dosage and Quantity Limits section below.</td>
</tr>
</tbody>
</table>

Dosage and Quantity Limits

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage and Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatasia (HPP)</td>
<td><strong>Perinatal/Infantile-onset HPP:</strong></td>
</tr>
<tr>
<td></td>
<td>• Recommended dosage regimen is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week. Injection site reactions may limit the tolerability of the six times per week regimen. The dose may be increased to 3 mg/kg three times per week for insufficient efficacy.</td>
</tr>
<tr>
<td></td>
<td><strong>Juvenile-onset HPP:</strong></td>
</tr>
<tr>
<td></td>
<td>• Recommended dosage regimen is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week.</td>
</tr>
</tbody>
</table>
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.

Asfotase alfa

Asfotase alfa (Strensiq®) 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.

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>03/14/17</td>
<td>New policy, 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>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera. All Rights Reserved.

**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.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - 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:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952, 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 S909, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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).

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。
請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avis sila a gen Enfòmasyon Enpòtan ladann. Avis sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w la oswa konsènan kouvèti asirans lan atravé Premera Blue Cross. Kapab genyen dat ki enpòtan nan avis sila a. Ou ka gen pou pran kék aksyon avan séten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

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).

Arabic (Arabic):

Deutsche (German):

Hmong (Hmong):

Iloko (Ilocano):
Daytoy a Pakdaak ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaak mabalini nga adda ket naglaon iti napateg nga impormasion maijanguwta ini aplikasyonwono yewo coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pesta ini daytoy a pakdaak. Mabalini nga adda rumbeng nga aramideny wono nga addang sakbay dagiti partikular a naulting nga adda alaw napato mapagatalainedyo nga coverage ti salun-atyo weny woytong kadagit yestos. Adda karbenganyo a mangala ini daytoy nga impormasion ken tlong iti bukodyo a pagasaa nga awani ta bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Premera Blue Cross

This notification contains important information. Premera Blue Cross will use this notification to communicate important information to you about your health insurance coverage. You should read and keep this notice for your records.

It is important that you take action within the deadlines indicated in this notice. Failure to take action could result in the loss of your health coverage.

Please call us at 800-722-1471 (TTY: 800-842-5357) if you have any questions about this notice or the contents of this notice.

한국어 (Korean):
본 통지서에는 중요한 정보가 포함되어 있습니다. 이 통지서는 귀하의 의료 보험 보장에 대한 중요한 정보를 전달하기 위해 사용됩니다. 이 통지서를 읽고 보관해 주십시오.

هذه الادعاء مثلها من الغلاف عند ما يتعلق بتغطية الرعاية الصحية.  يبلغ الدعم عن قيمة معينة من الفئة التي تغطيها الرعاية الصحية. هذه الدعم يمكن أن يكون من خلال خطة أو خطط أخرى. الرجاء الرجوع إلى الملف الخاصة بك للمزيد من المعلومات.

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении о страховой покрытии через Premera Blue Cross. В этом уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами.


Español (Spanish):
Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

ไทย (Thai):
ยังเป็นไปตามสิทธิ์ของคุณที่จะมีส่วนร่วมในการกำหนดระดับการเคลื่อนไหวของคุณในการรักษาสุขภาพของคุณผ่าน Premera Blue Cross และมีการปฏิบัติการในกรณีที่คุณจะต้องการรับการรักษาสุขภาพของคุณสำหรับคุณสมบัติที่คุณได้รับ โปรดติดต่อ Premera Blue Cross ที่ 800-722-1471 (TTY: 800-842-5357).

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує можливість того, що Вам треба буде здійснити передні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):