


## PHARMACY POLICY – 5.01.573

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

Effective Date:	Apr. 1, 2026	RELATED MEDICAL POLICIES:
Last Revised:	Mar. 10, 2026	None
Replaces:	N/A	

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## 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 Strensiq (asfotase alfa) is approved to treat perinatal/infantile- and juvenile-onset 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

Drug	Medical Necessity
<b>Strensiq (asfotase alfa)</b>	<p><b>Strensiq (asfotase alfa) may be considered medically necessary for the treatment of individuals with genetically confirmed perinatal/infantile- and juvenile-onset hypophosphatasia (HPP) when all the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>• The age of onset of disease is less than 18 years</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Genetic testing showing mutation status of the ALPL protein (gene encoding alkaline phosphatase)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Blood test showing age adjusted serum levels of alkaline phosphatase (ALP) are persistently below the lower limit of normal (i.e. present on at least 2 separate measurements) prior to 18 years of age</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Plasma pyridoxal 5'-phosphate (PLP) levels are greater than the upper limit of normal prior to 18 years of age</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Urinary phosphoethanolamine (PEA) are greater than the upper limit of normal prior to 18 years of age</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Skeletal radiographs support HPP prior to 18 years of age (e.g., rickets or bone deformities, osteomalacia, calcific periartthritis, atypical femoral fractures, recurrent metatarsal stress fractures)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Strensiq (asfotase alfa) is prescribed by or in consultation with a endocrinologist, geneticist, nephrologist, or rheumatologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The dose is limited to:               <ul style="list-style-type: none"> <li>○ Perinatal/infantile-onset HPP: 9 mg/kg per week</li> <li>○ Juvenile-onset HPP: 6 mg/kg per week</li> </ul> </li> </ul> <p><b>AND</b></p>



Drug	Medical Necessity
	<ul style="list-style-type: none"> <li>For members that weigh more than 40 kg, provider attests to permitting specialty pharmacy to determine vial strengths to minimize waste</li> </ul> <p><b>Note:</b> Strensiq is considered investigational for adult-onset HPP. For more information see <a href="#">Disease Background</a>.</p>

Drug	Investigational
<b>Strensiq (asfotase alfa)</b>	<p><b>All other uses of Strensiq (asfotase alfa) are considered investigational including use for adult-onset hypophosphatasia (HPP). For more information see <a href="#">Disease Background</a>.</b></p> <p><b>Strensiq (asfotase alfa) is subject to the product’s US Food and Drug Administration (FDA) dosage and administration prescribing information.</b></p>

Length of Approval	
Approval	Criteria
<b>Initial authorization</b>	<b>Strensiq (asfotase alfa) may be approved up to 12 months.</b>
<b>Re-authorization criteria</b>	<p><b>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 individual continues to show a positive clinical response to therapy as supported by one of the following:</b></p> <ul style="list-style-type: none"> <li>Skeletal radiographs</li> <li>Alkaline phosphatase (ALP)</li> <li>Plasma pyridoxal 5'-phosphate (PLP)</li> <li>Urinary phosphoethanolamine (PEA) levels</li> </ul>

Documentation Requirements
<p><b>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:</b></p>



## Documentation Requirements

- 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 B<sub>6</sub>. 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.

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.

Historically, hypophosphatasia (HPP) has been classified into the following subtypes based on the age of onset of clinical manifestations (12):

- Perinatal severe (perinatal onset)
- Perinatal benign (perinatal onset)
- Infantile (onset before 6 months of age)
- Childhood (onset between ages 6 months and 18 years)
- Adult (onset after 18 years of age)

Odontohypophosphatasia is a sixth subtype that may occur in children or adults. Its only clinical manifestations are dental defects, such as early tooth loss.

#### *Perinatal-Onset HPP:*

Severe and benign forms of perinatal HPP are typically identified on prenatal ultrasound demonstrating defective skeletal mineralization. The bones may appear short, bowed, and hypomineralized. In perinatal benign HPP, skeletal mineralization slowly improves spontaneously during late pregnancy or after birth, but in perinatal severe HPP, profound skeletal abnormalities and muscle weakness can lead to clinical consequences including stillbirth, postnatal death, and respiratory failure. Perinatal severe HPP is typically lethal in the neonatal period. Survivors often experience poor functional status and exhibit the following clinical findings: severe skeletal hypomineralization, respiratory insufficiency, hypercalcemia, hyperphosphatemia, nephrocalcinosis, and vitamin B6-dependent seizures.

#### *Infantile-Onset HPP*

Infantile HPP presents within the first six months of life in individuals who may not have had any clinical features apparent at birth. The clinical manifestations are severe and can be life-threatening but typically are not as critical as the perinatal form. Infantile HPP can be associated with increased mortality and may require extensive medical support. Key findings include failure to thrive, irritability and pain, premature craniosynostosis, rickets and fractures, respiratory



complications, nephrocalcinosis and nephrolithiasis, vitamin B6-dependent seizures, and muscle weakness.

### *Childhood- or Juvenile-Onset HPP*

Childhood or juvenile HPP usually manifest after six months of age and can vary widely in severity based on the degree of mineralization defects. The clinical findings in this age group may resemble rickets, and the severe end of the spectrum overlaps with infantile HPP. Additional findings include premature loss of primary teeth before age 5 years (particularly with intact root), short stature and skeletal deformities, fractures, delayed motor development, painful myopathies, and psychological disorders.

### *Adult-Onset HPP*

Adult-onset hypophosphatasia (HPP) typically presents in middle age and may have a wide range of clinical manifestations. The adult-onset HPP phenotype is generally milder than that of pediatric forms. In adults with HPP, signs and symptoms may be nonspecific. In its milder forms, HPP may be mistaken for osteoporosis. Key clinical findings include osteomalacia, fractures and pseudofractures, rheumatologic disorders, and nephrocalcinosis.

### *Diagnosis of HPP*

The diagnosis of HPP is a clinical diagnosis made on the basis of signs and symptoms as well as complications of HPP. It is supported by a persistently low ALP level adjusted for age and gender. Although most individuals with HPP have low ALP activity, most individuals with low serum ALP activity do not have HPP. A low ALP level requires further evaluation with the exclusion of other conditions or drugs which can contribute to a reduction in the ALP activity. These include drugs, such as anti-resorptive agents, excessive levels of vitamin D, as well as chemotherapy. Some diseases can also result in low ALP levels. These include hypoparathyroidism, hypothyroidism, hypercortisolism, renal osteodystrophy with adynamic bone disease, achondroplasia, Wilson's disease, and myeloma. Miscellaneous causes of low ALP include any severe illness or major surgery or trauma, massive transfusions, nutritional deficiencies, celiac disease, vitamin C deficiency, or zinc or magnesium deficiency. (13, 14)

Elevated levels of natural substrates of TNSALP can support the diagnosis of HPP and constitute major diagnostic criteria for childhood HPP. Elevated serum pyridoxal 5'-phosphate (PLP), the circulating form of vitamin B6, suggest HPP and result from impaired dephosphorylation of PLP to pyridoxal. The degree of PLP elevation roughly correlates with the degree of ALP deficiency. Elevated urinary phosphoethanolamine (PEA) may be helpful to support the diagnosis and to distinguish HPP from other causes of low ALP activity. Elevated levels of PEA are a biochemical marker of HPP, as TNSALP regulates the degradation of PEA to ethanolamine and inorganic



phosphate. Urinary PEA levels are generally higher in pediatric individuals with biallelic disease than in mildly affected adults and tend to correlate inversely with circulating liver, but not bone, TNSALP activity. (13, 14)

Imaging findings are important for both diagnosis and establishing the severity of disease and thus the approach to treatment. Perinatal HPP is often detected incidentally on routine prenatal sonogram. In infants and children with suspected HPP, imaging sites are selected based on clinical signs and symptoms. Plain radiographs have diagnostic value, as detection of skeletal demineralization with rachitic changes is a key criterion for diagnosis. (12)

## **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  $\geq 10\%$  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.

## 2024 Update

Reviewed Strensiq (asfotase alfa) prescribing information. Updated Strensiq (asfotase alfa) coverage criteria to include a prescriber requirement.

## 2025 Update

Reviewed Strensiq (asfotase alfa) prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.



## 2026 Update

Reviewed Strensiq (asfotase alfa) prescribing information. Updated disease background with additional diagnosis information, subtypes, and clinical signs and/or symptoms. Updated coverage criteria for Strensiq (asfotase alfa) adding a dosage limitation, and requirement for members that weigh more than 40 kg the provider attests to permitting specialty pharmacy to determine vial strengths to minimize waste. Updated throughout criteria reference from "at time of diagnosis" to "prior to 18 years of age." Updated alkaline phosphatase (ALP) requirement from blood test showing age adjusted serum levels of alkaline phosphatase (ALP) are below the lower limit of normal at time of diagnosis, to blood test showing age adjusted serum levels of alkaline phosphatase (ALP) are persistently below the lower limit of normal (i.e. present on at least 2 separate measurements) prior to 18 years of age. Updated skeletal radiograph examples to include rickets and recurrent metatarsal stress fractures, and specified atypical fractures as atypical femoral fractures. Updated specialist requirement removing doctor that specializes in treatment of hypophosphatasia or other related disorders, and listing nephrologist or rheumatologist. Updated initial authorization length of approval for all other reviews from 6 months to 12 months.

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## History

Date	Comments
04/01/17	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&T Committee, February 2017.
05/01/18	Annual Review, approved April 3, 2018. Added duration of authorization, reauthorization criteria and documentation requirements. Removed Dosage and Quantity Limit table.
09/21/18	Minor update. Added Consideration of Age statement.
05/01/19	Annual Review, approved April 18, 2019. No change to policy statement. Removed HCPCS code J3490, added J3590.
09/01/19	Interim Review, approved August 13, 2019. Updated Strensiq criteria and added additional criteria that support the diagnosis of hypophosphatasia. Removed HCPCS code J3590.
10/01//20	Annual Review, approved September 17, 2020. No change to policy statement.
01/01/22	Annual Review, approved December 2, 2021. No changes to policy statements.
12/01/22	Annual Review, approved November 7, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
06/01/23	Annual Review, approved May 22, 2023. No changes to policy statements.
04/01/24	Annual Review, approved March 12, 2024. Updated Strensiq (asfotase alfa) coverage criteria to include a prescriber requirement.



Date	Comments
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
04/01/26	Annual Review, approved March 10, 2026. Updated coverage criteria for Strensiq (asfotase alfa) adding a dosage limitation, and requirement for members that weigh more than 40 kg the provider attests to permitting specialty pharmacy to determine vial strengths to minimize waste. Updated throughout criteria reference from "at time of diagnosis" to "prior to 18 years of age." Updated alkaline phosphatase (ALP) requirement from blood test showing age adjusted serum levels of alkaline phosphatase (ALP) are below the lower limit of normal at time of diagnosis, to blood test showing age adjusted serum levels of alkaline phosphatase (ALP) are persistently below the lower limit of normal (i.e. present on at least 2 separate measurements) prior to 18 years of age. Updated skeletal radiograph examples to include rickets and recurrent metatarsal stress fractures, and specified atypical fractures as atypical femoral fractures. Updated specialist requirement removing doctor that specializes in treatment of hypophosphatasia or other related disorders, and listing nephrologist or rheumatologist. Updated initial authorization length of approval for all other reviews from 6 months to 12 months.

**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). ©2026 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.

