


PHARMACY POLICY – 5.01.573

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

Effective Date:	Apr. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Mar. 24, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [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 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

Drug	Medical Necessity
Strensiq (asfotase alfa)	<p>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:</p> <ul style="list-style-type: none"> • The onset of the disease is perinatal/infantile or juvenile (less than 18 years of age) <p>AND</p> <ul style="list-style-type: none"> • Genetic testing showing mutation status of the ALPL protein (gene encoding alkaline phosphatase) <p>AND</p> <ul style="list-style-type: none"> • Blood test showing age adjusted serum levels of alkaline phosphatase (ALP) below the lower limit of normal at time of diagnosis <p>AND</p> <ul style="list-style-type: none"> • Plasma pyridoxal 5'-phosphate (PLP) levels are greater than the upper limit of normal at time of diagnosis <p>OR</p> <ul style="list-style-type: none"> • Urinary phosphoethanolamine (PEA) are greater than the upper limit of normal at time of diagnosis <p>AND</p> <ul style="list-style-type: none"> • Skeletal radiographs at time of diagnosis supports HPP (e.g., bone deformities, osteomalacia, calcific periarthritis, or atypical fractures) <p>AND</p> <ul style="list-style-type: none"> • Strensiq (asfotase alfa) is prescribed by or in consultation with a geneticist, endocrinologist, or a physician who specializes in the treatment of hypophosphatasia or related disorders.

Drug	Investigational
Strensiq (asfotase alfa)	<p>All other uses of Strensiq (asfotase alfa) are considered investigational including use for adult-onset hypophosphatasia (HPP).</p> <p>Strensiq (asfotase alfa) is subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.</p>



Length of Approval	
Approval	Criteria
Initial authorization	<p>Non-formulary exception reviews for Strensiq (asfotase alfa) may be approved up to 12 months.</p> <p>All other reviews for Strensiq (asfotase alfa) may be approved up to 6 months.</p>
Re-authorization criteria	<p>Non-formulary exception reviews and all other reviews for 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 skeletal radiographs, alkaline phosphatase (ALP), plasma pyridoxal 5'-phosphate (PLP) and/or urinary phosphoethanolamine (PEA) levels.</p>

Documentation Requirements
<p>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:</p> <ul style="list-style-type: none"> 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 $\geq 10\%$ 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.

References

1. Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med*. 2012;366:904-13.
2. Whyte MP, Rockman-Greenberg C, Ozono K, et al. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. *J Clin Endocrinol Metab*. 2016;101:334-42.
3. Mornet E, Nunes ME. Hypophosphatasia. In *GeneReviews* [Internet]. Accessed March 11, 2025.
4. Strensiq (asfotase alfa) injection prescribing information. Alexion Pharmaceuticals, Inc.; Cheshire, CT. Revised July 2024.
5. National Institute for Health and Care Excellence (NICE). Benefits of new drug to treat rare inherited bone disorder too uncertain to justify its high cost says NICE in draft guidance. Dec 3, 2015. Accessed March 11, 2025.
6. Whyte M, Fujita K, Moseley S, Thompson D, McAlister W. Validation of a novel scoring system, the Radiographic Global Impression of Change (RGI-C) Scale, for assessing skeletal manifestations of hypophosphatasia in infants and children (abstract). Poster presented at the American Society for Bone and Mineral Research, Seattle, October 12. Abstract MO059.
7. Thacher T, Fischer P, Pettifor J, Lawson J, Manaster B, Reading J. Radiographic scoring method for the assessment of the severity of nutritional rickets. *J Trop Pediatr*. 2000;46(3):132-9.



8. Deitz JC, Kartin D, Kopp K. Review of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2). Phys Occup Ther Pediatr [Internet]. 2007 Jan;27(4):87–102.. Accessed March 11, 2025.
9. Mornet E. Hypophosphatasia. Orphanet J Rare Dis. 2007; 2:40. Accessed March 11, 2025.
10. Scott LJ. Asfotase alfa: a review in paediatric hypophosphatasia. Drugs. 2016;76:255–62.
11. Simon S, Resch H, Klaushofer K, et al. Hypophosphatasia: From Diagnosis to Treatment. Curr Rheumatol Rep. 2018 Sep 10;20(11):69.
12. Kishnani PS, Rockman-Greenberg C, Rauch F, et al. Five-year efficacy and safety of asfotase alfa therapy for adults and adolescents with hypophosphatasia. Bone. 2019;121:149. Epub 2018 Dec 18.

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.
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



Date	Comments
	months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

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). ©2025 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.

