BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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STRENSIQ® (asfotase alfa) solution for subcutaneous injection

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Strensiq (asfotase alfa) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a physician experienced in the care of individuals with HPP (e.g., pediatric endocrinologist, metabolic bone disease specialist)

  2. Individual is 18 years old or less

  3. A confirmed diagnosis of **ONE** of the following:
     a. Perinatal/infantile-onset hypophosphatasia (HPP)
     b. Juvenile-onset HPP

  4. There is documentation of disease symptom onset before 18 years of age

  5. At age of disease onset, individual had clinical manifestations consistent with hypophosphatasia such as vitamin B6 dependent seizures, skeletal abnormalities (rachitic chest, bowed arms/legs), muscle weakness, hypotonia, poor feeding or failure to thrive, respiratory insufficiency, premature tooth loss, delayed walking, waddling gait, low trauma fractures

  6. At age of disease onset, individual had radiographic imaging to support diagnosis of hypophosphatasia (such as infantile rickets, alveolar bone loss, craniosynostosis, nontraumatic fractures)

  7. Genetic testing to determine a gene mutation in **ONE** or more of the following genes:
     a. Alkaline phosphatase liver/bone/kidney (ALPL) gene
     b. Tissue-nonspecific alkaline phosphatase (TNSALP) gene

  8. Individual has an unfractionated serum alkaline phosphatase (ALP) level below the age and gender-adjusted normal range (in the absence of bisphosphonate therapy

  9. Individual has elevated level of tissue non-specific alkaline phosphatase (TNSALP) substrates:
     a. Serum pyridoxal 5'-phosphate [PLP] level (vitamin B6)
     b. Serum or urine phosphoethanolamine [PEA] level
     c. Urinary inorganic pyrophosphate [PPi] level

  10. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
      a. Ophthalmologic examination
      b. Renal ultrasound
      c. At time of onset, serum calcium, phosphate levels are within the age-adjusted normal range or elevated

  Initial approval duration: 12 months

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- **Criteria for continuation of coverage (renewal request):** Strensiq (asfotase alfa) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a physician experienced in the care of individuals with HPP (e.g., pediatric endocrinologist, metabolic bone disease specialist)

2. Individual's condition responded while on therapy. Response is defined as:
    a. **For Perinatal/ Infantile-Onset HPP: THREE** of the following:
        i. Survival
        ii. Ventilation-free survival
        iii. Improvement in height/weight
        iv. No Fractures
        v. Radiographic Global Impression of Change (RGI-C) score of +2 or higher
        vi. Clinically relevant decrease from baseline in tissue non-specific alkaline phosphatase (TNSALP) substrates:
            1. Serum pyridoxal 5'-phosphate [PLP]
            2. Serum or urine phosphoethanolamine [PEA]
            3. Urinary inorganic pyrophosphate [PPi]

    b. **For Juvenile-Onset HPP: Clinical improvement with multiple objective findings THREE** of the following:
        i. Functionality retains most activities of daily living for individual's age
        ii. Improvement in height/weight
        iii. Radiographic Global Impression of Change (RGI-C) score of +2 or higher
        iv. Clinically relevant decrease from baseline in tissue non-specific alkaline phosphatase (TNSALP) substrates:
            1. Serum pyridoxal 5'-phosphate [PLP]
            2. Serum or urine phosphoethanolamine [PEA]
            3. Urinary inorganic pyrophosphate [PPi]
        v. Increase in Gait/Mobility defined as **ONE** of the following:
            1. Increase in 6MWT over baseline
            2. Improvement in modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) over baseline

3. Individual has been adherent with the medication

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Ectopic calcification of the eye
        ii. Ectopic calcification of the kidneys
        iii. Severe hypersensitivity reaction

5. There are no significant interacting drugs

Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Strensiq (asofatse alfa) is a tissue non-specific alkaline phosphatase indicated for the treatment of patients with perinatal/infantile-onset hypophosphatasia (P/I-HPP) and juvenile-onset hypophosphatasia (J-HPP). It is a recombinant form of alkaline phosphatase, which is a soluble glycoprotein composed of two identical polypeptide chains. Each chain consists of the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), the human immunoglobulin G Fc domain and a deca-aspartate peptide used as a bone targeting domain.

Hypophosphatasia (HPP) is a bone disorder caused by genetic mutations that result in low levels of enzymes needed to harden bone. HPP is the rare inborn-error-of-metabolism characterized enzymatically by low activity of the tissue nonspecific isoenzyme of alkaline phosphatase (TNSALP) and caused by loss-of-function mutation(s) in the alkaline phosphatase liver/bone/kidney (*ALPL*) gene, the gene that encodes this cell-surface phosphohydrolase. TNSALP catalyzes the extra-cellular dephosphorylation of inorganic pyrophosphate (PPi) to inorganic phosphate (Pi). Strensiq (asofatse alfa) works by replacing the deficient enzyme associated with HPP. The alkaline phosphatase gene helps maintain phosphate levels required for bone formation, brain, and muscle function.

The deficiency in TNSALP enzyme activity leads to elevations in several TNSALP substrates, including inorganic pyrophosphate (PPi). Elevated extracellular levels of PPi block hydroxyapatite crystal growth that inhibits bone mineralization and causes an accumulation of bone matrix that manifests as rickets and bone deformation in infants and children and as osteomalacia once growth plates close, along with muscle weakness in adults.

The TNSALP enzyme also has a role in dephosphorylating pyridoxal-5'-phosphate (PLP), the major circulating form of vitamin B6, to pyridoxal (PL). Dephosphorylation is essential to allow PL to enter cells within the CNS. Once PL enters cells within the CNS, it is rephosphorylated to PLP and contributes as a cofactor in a number of enzymatic reactions, including the formation of neurotransmitters such as gamma-aminobutyric acid (GABA). GABA is an inhibitory neurotransmitter, and reductions in GABA activity can lead to unopposed excitatory neurotransmitter activity, which can cause seizures. Accumulation of phosphoethanolamine (PEA), a degradation product of cell surface phosphatidylinositol-glycan anchors also occurs.

Management of HPP at all ages focuses on supportive therapy to minimize complications of the disease including treatment of seizures, adequate dental care, and medications for pain relief.

Mortality from HPP is reported to be 50-100% within the first year of life in the most severely affected patients (perinatal- or infantile-onset HPP) with respiratory failure the most common cause of death in infants with HPP. In patients surviving to adolescence and adulthood, long-term clinical sequelae of disease include recurrent and non-healing fractures, weakness, arthritis, dependence on internal fixation devices (due to the risk of recurrent

fracture), severe and often refractory pain, and the requirement for ambulatory assistive devices (wheelchairs, wheeled walkers and canes).

The clinical presentation of HPP is a result of the accumulation of TNSALP substrates, and the resulting imbalance in calcium and phosphate metabolism. The clinical presentation of HPP can be highly variable, progressive, and potentially life-threatening, leading to progressive and debilitating damage to multiple vital organs, including bone deformity, pain and muscle weakness, respiratory failure, seizures, nephrocalcinosis, and dental abnormalities.

There are at least 300 disease-causing mutations in the *ALPL* gene with both autosomal dominant and recessive inheritance patterns. The key diagnostic factor for HPP is low serum alkaline phosphatase (ALP). HPP can be diagnosed when an age and gender-adjusted low serum ALP level is accompanied by evidence from medical history and physical/radiologic findings suggestive of HPP. Elevated levels of substrates of TNSALP, including serum PPi (if available) and PLP, and urine PEA may aid in confirming the diagnosis. Unlike patients with most forms of rickets or osteomalacia, patients with HPP do not have low serum calcium and serum levels of the bioactive forms of vitamin D and parathyroid hormone (PTH) are typically normal

Other skeletal disorders must be ruled out include rickets, osteogenesis imperfect, dentinogenesis imperfect and periodontal disease, osteoarthritis, idiopathic osteoporosis, and Paget's disease

The diagnosis of HPP is made when a patient has low ALP activity (age and gender adjusted), elevated PLP (vitamin B6) or elevated PEA along with skeletal and muscular evidence. Serum ALP normal reference ranges are higher in infants, children, and adolescents than they are in adults. Laboratories vary in their age-appropriate reference ranges; therefore, serum or plasma ALP activity must be interpreted based upon laboratory-specific reference ranges. ALP is used as a detection reagent in many laboratory tests and the presence of asfotase alfa in clinical laboratory samples could result in erroneous test results, laboratory personnel should use an alternative testing platform for patients on treatment. Serum ALP measurements are expected to be elevated during treatment and may be unreliable for making clinical decisions.

Radiographic evidence of HPP include manifestations of abnormal mineralization in provisional zones of the long bones, knocked/bowed knees, muscle weakness, musculoskeletal pain, fractures, poor growth, and premature tooth loss with roots intact. Musculoskeletal aspects of HPP can impair mobility and ambulation, which may have implications for activities of daily living, community participation, and quality of life. The Radiographic Global Impression of Change (RGI-C) score is a tool for scoring radiographic changes over time in key features of HPP in pediatric patients. RGI-C is valid and reliable for detecting clinically important changes in skeletal manifestations of severe HPP in newborns, infants, and children, including during asfotase alfa treatment. Clinical trials of asfotase alfa defined response to treatment as achieving a RGI-C score of +2 or higher.

The Performance-Oriented Mobility Assessment (POMA) is a validated tool for evaluating gait and balance in elderly and community-dwelling adults. The POMA gait subtest (POMA-G) contains components that can be applied directly or indirectly to measure gait impairments (e.g., trunk sway, walking stance, step continuity) in patients with HPP. Clinical trials of asofatase alfa also used an evaluation of a 6-minute Walk test (6MWT) to assess mobility in juvenile-onset HPP, the results showed patients were able to walk longer distances when compared to baseline values.

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Definitions:

Major sub-types of HPP:

Onset	Type	Features
In utero	Perinatal	Hypomineralization; osteochondral spurs; respiratory insufficiency
Post-natal to 6 months	Infantile	Hypomineralization; rachitic ribs; failure to thrive; hypercalciuria and hypercalcemia; respiratory compromise; craniosynostosis, increased intracranial pressure, papilledema; vitamin B6 responsive seizures; premature loss of deciduous teeth
> 6 months to 18 years	Childhood/Juvenile	Short stature; rachitic deformities – bowed legs or knock-knees, enlargement of wrists, knees, and ankles; walking delayed; waddling gait; severe bone and muscle pain; non-traumatic fractures; premature loss of deciduous teeth
> 18 years	Adult	Stress fractures, mainly metatarsal; osteomalacia; chondrocalcinosis; osteoarthritis; pseudofractures; severe bone and muscle pain; pseudogout

Clinical features of HPP:

- Abnormally shaped chest
- Defects in dentin (e.g., dental abscesses; early tooth decay)
- Enthesopathy (e.g., calcification of tendons, ligaments and joint capsules)
- Hyperphosphatemia
- Hypertension
- Hypophosphatemia
- Muscle weakness and myopathy
- Nephrocalcinosis
- Rickets due to hereditary hypophosphatasia
- Short limbs
- Slow growth
- Unexplained fractures

Radiographic Global Impression of Change (RGI-C) scale:

Radiographic Global Impression of Change (RGI-C) scale						
Worsening			No change	Healing		
Severe	Moderate	Mild		Minimal	Substantial	Complete or near complete
-3	-2	-1	0	+1	+2	+3

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Performance-Oriented Mobility Assessment – Gait (POMA-G):

The mPOMA-G Scale (modified POMA-G)		
Observation		**Score**
Step length and height	*Right swing foot:*	
	– Does not pass the left stance foot with step	0
	– Right heel passes the left stance foot	1
	– Right foot passes the left stance foot by at least the length of individual's foot between the stance toe and swing heel	2
	Right foot clear:	
	– Right foot does not clear floor completely with step or raises foot by more than 1–2 inches	0
	– Right foot completely clears floor	1
	Left swing foot:	
	– Does not pass the right stance foot with step	0
	– Left heel passes the right stance foot	1
	– Left foot passes the right stance foot by at least the length of individual's foot between the stance toe and swing heel	2
	Left foot clear:	
	– Left foot does not clear floor completely with step or raises foot by more than 1–2 inches	0
	– Left foot completely clears floor	1
Step symmetry	– Right and left step length not equal (estimate)	0
	– Right and left step appear equal	1
Step continuity	– Stopping or discontinuity between steps	0
	– Steps appear continuous unilaterally (observe raising heel of 1 foot as heel of other foot touches the floor unilaterally) or flat foot contact on stance limb when heel of other foot touches the floor bilaterally, no breaks or stops in stride	1
	– Steps appear continuous bilaterally (observe raising heel of 1 foot as heel of other foot touches the floor, bilaterally), no breaks or stops in stride, step lengths equal	2
Trunk	– Marked sway or uses walking aid. Marked sway = moderate lateral flexion as the result of instability bilateral or unilateral	0
	– No marked sway but flexion of knees or back or spreads arms out while walking compensatory patterns, such as trunk flexion, knee flexion, arm abduction, or retraction to increase postural stability while walking	1
	– No sway, no flexion, no use of arms, and no walking aid	2
Walk stance	– Heels always apart, wide base of support utilized to increase postural stability	0
	– Heels intermittently apart or almost touching while walking	1
Initiation of gait	– Any hesitancy or multiple attempts	0
	– No hesitancy	1
Path	– Marked deviation	0
	– Mild/moderate deviation or uses walking aid	1
	– Straight without walking aid	2
GAIT SCORE		/12

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Resources:

Strensiq (asfotase alfa) product information, revised by Alexion Pharmaceuticals, Inc. 06-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 12, 2021.

Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. N Engl J Med. Mar 8 2012;366(10):904-913. Accessed April 11, 2019. Re-reviewed July 13, 2021.

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Phillips D, Griffin D, Przybylski T, et al.: Development and validation of a modified performance-oriented mobility assessment tool for assessing mobility in children with hypophosphatasia. J Pediatric Rehabilitation Medicine: An Interdisciplinary Approach 2018 (11): 187–192. Accessed April 10, 2019. Re-reviewed July 13, 2021.