BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

STRENSIQ® (asfotase alfa) subcutaneous injection Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Strensiq (asfotase alfa) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** 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 hypophosphatasia (HPP) (e.g., pediatric endocrinologist, metabolic bone disease specialist)

2. Individual has a confirmed diagnosis of **ONE** of the following:
   a. Perinatal/infantile onset hypophosphatasia (HPP) who has/had onset of signs and symptoms before 6 months of age

   b. Juvenile-onset HPP who has/had onset of symptoms before 18 years of age

3. Individual has **clinical manifestations** (e.g., vitamin B6 dependent seizures, skeletal abnormalities (such as 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) consistent with hypophosphatasia onset ≤ 18 years of age (required to support the diagnosis) (see Definitions section)

4. Individual has **radiographic imaging** (e.g., infantile rickets, alveolar bone loss, craniosynostosis, nontraumatic fractures) consistent with hypophosphatasia onset ≤ 18 years of age (required to support the diagnosis) (see Definitions section)

5. Individual has **laboratory evidence** of an unfractionated serum alkaline phosphatase (ALP) level **below** the age and gender-adjusted normal range (in the absence of bisphosphonate therapy) (see Definitions section)

6. Individual has elevated level of **ONE** of the following tissue non-specific alkaline phosphatase (TNSALP) substrates:
    a. Serum pyridoxal 5'-phosphate [PLP] level (vitamin B6) without oral supplementation
    b. Serum or urine phosphoethanolamine [PEA] level
    c. Urinary inorganic pyrophosphate [PPi] level

7. Individual **with** suggestive clinical, laboratory, and radiographic findings for HPP with **ONE** of the following on molecular genetic testing:
    a. Biallelic (homozygous or compound heterozygous) loss-of-function alkaline phosphatase liver/bone/kidney (ALPL) gene variant
    b. A heterozygous ALPL gene variant with dominant-negative effect

8. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

9. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Documentation of recent weight to ensure accurate weight-based dosing (within prior 1 month)
    b. Ophthalmologic examination looking for conjunctival and corneal calcification
    c. Renal ultrasound looking for nephrocalcinosis and nephrolitiasis
    d. Serum calcium, phosphate levels are within the age-adjusted normal range or elevated

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Strensiq (asfotase alfa) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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 hypophosphatasia (HPP) (e.g., pediatric endocrinologist, metabolic bone disease specialist)

2. Individual's condition has responded while on therapy with response defined as the following:

a. **For Perinatal/ Infantile-Onset HPP: FOUR** 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, FOUR** 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. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

~~4.~~5. Prescriber has submitted recent weight to ensure accurate weight-based dosing (within prior 1 month)

~~4.~~6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Ectopic calcification of the eye
   b. Ectopic calcification of the kidneys
   c. Severe hypersensitivity reaction
   d. Possible immune-mediated clinical effect due to development of anti-asfotase alpha antibodies and neutralizing antibodies in an individual who developed recurrence or worsening after an initial therapeutic response (antibody testing to be done by contacting manufacturer)

Renewal duration: 12 months
Note: Some Strensiq-treated patients with initial therapeutic response to Strensiq subsequently developed worsening in disease-associated laboratory and radiographic biomarkers (some in association with neutralizing antibodies) suggesting possible immune-mediated effects on Strensiq' s pharmacologic action resulting in disease progression. The effect of anti-asfotase alfa antibody formation on the long-term efficacy

of Strensiq is unknown. There are no marketed anti-asfotase alfa antibody tests. If individual experiences progression of HPP symptoms or worsening of disease-associated laboratory and imaging biomarkers after a period of initial therapeutic response to Strensiq, consider obtaining anti-asfotase alfa antibody testing by contacting Strensiq Medical Information at Alexion at 1-888-765-4747 or by email at medinfo@alexion.com.

- 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 Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Description:

Strensiq (asfotase 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 asfotase 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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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; pseudo fractures; severe bone and muscle pain; pseudogout

Clinical features:

- Clinical features of infantile rickets: growth failure, craniotabes, craniosynostosis, blue sclerae, flail chest, costochondral enlargement ("rachitic rosary"), scoliosis, thickening of wrists, knees, and ankles, bowing of legs, lax ligaments, and hypotonia
- Premature loss of deciduous teeth beginning with the incisors. Unusually and characteristically, the dental root remains attached to the lost tooth. Dental caries and early loss or extraction of adult teeth is also seen
- Vitamin B_6 (pyridoxine)-responsive seizures
- Bone pain

Laboratory features:

- Hypercalciuria particularly during the first year of life with or without hypercalcemia
- Typically, normal serum calcium and ionized calcium. Note: May be elevated, particularly in the first year of life
- Typically, normal serum and urine inorganic phosphate. Note: May be elevated
- Normal serum vitamin D (25-hydroxy and 1,25-dihydroxy) and parathyroid hormone
- Elevated plasma vitamin B_6 without oral supplementation
- Elevated serum pyridoxal 5'-phosphate (PLP), a biologically active metabolite of vitamin B_6. Note: (1) Reference laboratories may measure PLP and report as "vitamin B_6." (2) Use of multivitamin or calcium supplements containing vitamin B_6 within a week of assaying serum PLP may lead to false positive results
- Elevated urine phosphoethanolamine (PEA) and proline on urine amino acid chromatogram. Note: (1) Urine PEA may be elevated with other metabolic bone diseases. (2) Urine PEA may be normal in affected individuals and can be elevated in asymptomatic heterozygotes
- Elevated urine inorganic pyrophosphate (PPi). Note: (1) Assay is not available in North American clinical laboratories. (2) Asymptomatic heterozygotes can have elevated urine PPi
- Reduced serum unfractionated alkaline phosphatase (ALP) activity. Note: (1) Transient increases in serum ALP activity can occur during pregnancy, with liver disease, and after acute fracture or surgery.

Thus, serial measurements may be necessary in toddlers with unexplained fractures. Quantitation of the activity of the bone isoform of ALP in serum may be necessary in the setting of liver disease. The bone isoform is heat labile; the liver isoform is heat stable. (2) Asymptomatic heterozygotes can have reduced serum ALP activity

Radiographic features:

- Prenatal long bone bowing with osteochondral spurs
- Infantile rickets: under mineralized bones, widened-appearing sutures, brachycephaly, rachitic costochondral rib changes, flared metaphyses, poorly ossified epiphyses, and bowed long bones
- Focal bony defects of the metaphyses resembling radiolucent "tongues" are fairly specific for childhood hypophosphatasia
- Defective mineralization of growing/remodeling bone and/or teeth. Bone mineral content increases with age, and there may be improved mineralization during adolescence with decreased mineralization in middle age
- Alveolar bone loss resulting in premature loss of deciduous teeth typically involving the anterior mandible, with the central incisors lost first. However, any tooth may be affected
- Pathologic fractures. Growing children may have a predilection to metaphyseal fractures; however, epiphyseal and diaphyseal fractures are also seen. In adults, metatarsal stress fractures and femoral pseudofractures prevail
- Unexplained fractures
- Osteomalacia with lateral pseudofractures ("Looser zones") in adult hypophosphatasia

Other features of HPP:

- Enthesopathy (e.g., calcification of tendons, ligaments, and joint capsules)
- Muscle weakness and myopathy
- Nephrocalcinosis
- Rickets due to hereditary hypophosphatasia
- Short limbs
- Slow growth

Diagnostic criteria for HPP in adults and children with persistently low ALP:

Diagnostic criteria for HPP in adults (2 major or 1 major and 2 minor)

Major

- Pathogenic or likely pathogenic *ALPL* gene variant
- Elevation of natural substrates (*measurement of plasma vitamin B6 requires stopping pyridoxine supplementation 1 week prior to measurement*)
- Atypical femoral fractures (pseudofractures)
- Recurrent metatarsal fractures

Minor

- Poorly healing fractures
- Chronic musculoskeletal pain
- Early atraumatic loss of teeth
- Chondrocalcinosis

- Nephrocalcinosis

Diagnostic criteria for HPP in children (2 major or 1 major and 2 minor)

Major

- Pathogenic or likely pathogenic *ALPL* gene variant
- Elevation of natural substrates (*measurement of plasma vitamin B6 requires stopping pyridoxine supplementation 1 week prior to measurement*)
- Early nontraumatic loss of primary teeth
- Presence of rickets on radiographs

Minor

- Short stature or linear growth failure over time
- Delayed motor milestones
- Craniosynostosis
- Nephrocalcinosis
- B6 responsive seizures

Normal ALP ranges by age and gender:

Age	Male (IU/L)	Female (IU/L)
0 to 5 day	47−127	47−127
6 to 10 day	29−242	29−242
11 to 20 day	109−357	109−357
21 to 30 day	94–494	94–494
1 to 2 month	149−539	149−539
3 to 6 month	131−452	131−452
7 to 11 month	117−401	117−401
12 m to 6 year	158−369	158−369
7 to 12 year	150−409	150−409
13 year	156−435	78−227
14 year	114−375	64−161
15 year	88−279	56−134
16 year	74−207	51−121
17 year	63−161	47−113
18 to 20 year	51−125	42−106
>20 year	44−121	44−121

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

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. 03-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 23, 2024.

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