Strensiq (asfotase alpha) Prior Authorization Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agents	FDA Labeled Indications	Dosage
Strensiq® (asfotase alfa) Injection	• Perinatal/Infantile-onset hypophosphatasia	**Perinatal/Infantile-onset hypophosphatasia:** 2 mg/kg subcutaneously three times per week or 1 mg/kg subcutaneously six times per week. The dose of Strensiq may be increased for lack of efficacy (e.g., no improvement in respiratory status, growth, or radiographic findings) up to 9 mg/kg per week administered as 3 mg/kg subcutaneously three times per week
	• Juvenile-onset hypophosphatasia	**Juvenile-onset hypophosphatasia:** 2 mg/kg subcutaneously three times per week or 1 mg/kg six times per week Injection site reactions may limit the tolerability of the six times per week regimen in both Perinatal/Infantile and Juvenile-onset hypophosphatasia

CLINICAL RATIONALE

Hypophosphatasia (HPP) is a rare genetic disease, characterized by mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene, leading to a diminished activity of the TNSALP enzyme in target tissues and accumulation on TNSALP substrates, including inorganic pyrophosphate, an inhibitor of mineralization.[2,5] TNSALP controls skeletal and dental mineralization by hydrolyzing inorganic pyrophosphate, an inhibitor of hydroxyapatite crystal growth. Insufficient activity can lead to chest wall instability and respiratory complications in perinatal and infantile forms. Natural substrates of TNSALP that accumulate in

hypophosphatasia include inorganic pyrophosphate (PPi), phosphoethanolamine (PEA), and pyridoxal 5'-phosphate (PLP), the principal circulating form of vitamin B6.[4]

Perinatal HPP features extreme skeletal disease obvious at birth; survival beyond birth is rare. Infantile HPP develops prior to 6 months of age and has an estimated 50% mortality during infancy typically due to respiratory complications. Patients develop rickets, failure to thrive, hypotonia, myopathy, and is often complicated by hypercalcemia, nephrocalcinosis, craniosynostosis, and vitamin B6-dependent seizures. Although spontaneous improvement sometimes occurs in infantile hypophosphatasia, substantial bone disease and weakness often persist. Skeletal deterioration typically results in death from respiratory insufficiency. In both forms, hypo-mineralization leads to thoracic instability, fractures, and deformities, and sometimes even pulmonary hypoplasia in perinatal HPP.[3]

Juvenile HPP tends to be less severe than those that appear in infancy. Affected children may have short stature, bowed legs, enlarged wrist and ankle joints (metaphyseal flares that appear as "swollen joints"), muscle weakness, and abnormal skull shape.[3]

Although the disease spectrum is a continuum, six clinical forms are usually recognized based on age at diagnosis and severity of features:[3]

Clinical Form	Bone Symptoms	Dental Symptoms	Clinical Diagnosis
Perinatal lethal	Hypo-mineralization Osteochondral spurs	NA	Radiographs Ultrasonography
Prenatal benign	Bowing of long bones	NA	Ultrasonography Clinical examination
Infantile	Craniosynostosis Hypo-mineralization Rachitic ribs Hypercalciuria	Premature loss of deciduous teeth	Clinical examination Biology (serum AP activity, PEA, and PLP) Radiographs
Childhood	Short stature Skeletal deformity Waddling gate Bone pain/fractures	Premature loss of deciduous teeth	Clinical examination Biology (serum AP activity, PEA, and PLP) Radiographs
Adult	Stress fractures: metatarsal, tibia Osteoarthritis		Clinical examination Biology (serum AP activity, PEA, and PLP) Radiographs
Odotohypophosphatasia	Loss of alveolar bone	Exfoliation (incisors) Reduced thickness of the dentin Enlarged pulp chambers of teeth	Clinical examination Biology (serum AP activity, PEA, and PLP)

		Dental caries	

A diagnosis of HPP is based upon identification of characteristic signs and symptoms, a detailed patient history, a thorough clinical evaluation, and a variety of laboratory tests including routine x-ray and biochemical studies. Proper diagnosis of HPP is easy for physicians who are familiar or experienced with this disorder. However, most physicians have little or no knowledge of HPP. Consequently, affected individuals and families may face a frustrating delay in diagnosis. Now, mutation analysis of the *ALPL* gene is available from commercial laboratories.

Clinical Testing and Workup[4]

The diagnosis is rarely first suspected from a routine panel of biochemical tests that includes measuring the activity of alkaline phosphatase in blood. Instead signs and symptoms have led to this routine test where the low levels of alkaline phosphatase must be recognized. Individuals with HPP have reduced serum alkaline phosphatase activity for their age, except for the extremely rare individual with pseudohypophosphatasia who has normal activity levels. Identification of deficient alkaline phosphatase activity is consistent with HPP, but not conclusive since other conditions can result in this finding. Additionally, some individuals who are genetic carriers of HPP, but who do not develop any symptoms of the disorder, may also have low blood ALP levels.

Importantly, the range of serum ALP activity varies by age. Healthy children normally have higher ALP levels than healthy adults. If the laboratory doing the testing only gives the normal range of ALP activity in adults in its report, a diagnosis of HPP in a child can be missed because the child's ALP activity will mistakenly be believed to be normal.

In the U.S. and elsewhere, a suspected diagnosis of HPP can be further supported by measuring the serum level of vitamin B6. This test is performed by several commercial laboratories. Individuals with HPP have elevated levels of pyridoxal 5'-phosphate (PLP: the active form of vitamin B6) in the blood because PLP is normally broken down by TNSALP. PLP is elevated even in individuals with mild HPP. However, some genetic carriers of HPP who do not develop any symptoms can have an elevated PLP level as well. In the past, blood or urine was tested for increased amounts of phosphoethanolamine (PEA), another chemical normally broken down by TNSALP. However, this finding is not specific to HPP and can occur because of other metabolic bone diseases. Additionally, some individuals with HPP have normal PEA levels. Screening for elevated PLP is preferred over screening for PEA because it is more sensitive, more precise, and less expensive.

In the most severe cases of HPP, specifically the perinatal and infantile forms, x-ray studies can reveal diagnostic changes within the bones. However, these changes may not be recognized as being associated with HPP, except by radiologists familiar with the disorder.

Molecular genetic testing can support a diagnosis of HPP. Molecular genetic testing can detect mutations in the *ALPL* gene known to cause the disorder, but it is only available as a diagnostic service at specialized laboratories.

Additional assessments should be performed to identify a lack of improvement or treatment failure in patients receiving asfotase alfa. For infants who do not exhibit skeletal improvements after 3 – 6 months of treatment (or in children after 6-9 months) or for children who stop having improvement in mineralization and/or show recurrence of symptoms, additional radiographs and laboratory tests, including ALP, PLP, PTH, calcium, vitamin d, PO_4, magnesium, urine calcium/creatine ratio can be performed. Immunoglobulin G (IgG) anti-asfotase alfa antibody testing is not currently commercially available; it is available for research use only and through the HPP registry. Weight and length/height in infants and children should increase steadily and progress along percentile lines during

treatment with asfotase alfa. If growth is not observed, inadequate nutrition or development of musculoskeletal conditions, such as scoliosis, should be considered. Similarly, the lack of an increase in head circumference should prompt further investigation of possible craniosynostosis. It is also important to assess the role of antibodies and compliance in a patient with perceived treatment failure.[6]

Efficacy[1]
Strensiq is the first approved therapy for perinatal, infantile and juvenile-onset HPP. Strensiq is a formulation of asfotase alfa, which is a soluble glycoprotein composed of two identical polypeptide chains. Strensiq is a tissue nonspecific alkaline phosphatase produced by recombinant DNA technology in a Chinese hamster ovary cell line.

Strensiq was evaluated in 2 studies for perinatal/infantile-onset hypophosphatasia (HPP) identified in the label as study 1 and study 2.

Study 1 was a 24-week prospective single-arm trial in 11 patients with severe perinatal/infantile-onset HPP. Study 2 was a prospective open-label study in 59 patients with perinatal/infantile-onset HPP. Survival and invasive ventilation-free survival were compared in both study 1 and study 2 with a historical cohort of untreated patients with similar clinical characteristics.

In the Strensiq treated populations, 91% were alive at the point of last contact vs 27% of historical controls (Hazard Ratio 0.14, 95% confidence interval). The Kaplan-Meier estimate of alive at age 1 year (week 48) was 97% in the Strensiq treated populations and 42% in the historical controls.

The percentage of patients that were alive and not on ventilation at the point of last contact was 85% in the Strensiq treated population and 25% in the historical controls (Hazard Ratio 0.21, 95% confidence interval). The Kaplan-Meier estimate of alive and not on ventilation at age 1 year (week 48) was 96% in the Strensiq treated population and 31% in the historical controls.

Study 3 (as identified in the prescribing information) was a prospective open-label 24-week trial that included 8 juvenile-onset HPP and 5 perinatal/infantile onset HPP patients. Growth and skeletal manifestations were compared with a historical cohort of 32 untreated patients with similar clinical characteristics. Strensiq treated patients showed better z-scores for height and weight compared to the historical cohorts. All 8 Strensiq treated patients were rated as responders (defined as a 2 or higher on the Radiographic Global Impression of Change scale by month 54) of treatment for skeletal manifestations.

Gait was also assessed using a modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale in all 8 patients and using the 6-minute walk test in 7 of the 8 patients in this study. Step length improved by at least 1 point in either foot in 6 out of the 8 patients compared to 1 out of 6 control patients. The proportion of patients who had 6-minute walk test percent predicted values within the normal range for age, sex, and height-matched peers increased from 0 out of 8 patients at baseline to 6 patients by month 48. All 6 of these patients were also able to walk longer distances at this time point compared to baseline.

Prenatal/infantile and juvenile-onset HPP patients treated with Strensiq had reductions in plasma TNSALP substrates, PPi and PLP within 6 to 12 weeks of treatment. Reductions in plasma PPi and PLP levels did not correlate with clinical outcomes.

Safety[1]

The 80 mg/0.8 mL vial of Strensiq should not be used in pediatric patients weighing less than 40 kg because the systemic exposure of asfotase alfa achieved with the 80 mg/0.8 mL (higher concentration) is lower than that achieved with the other strength vials (lower concentration). A lower exposure may not be adequate for this subgroup of patients. Patients with HPP are at increased risk for developing ectopic calcifications. Events of ectopic calcification, including ophthalmic and renal, have been reported in clinical trials experience with Strensiq. Although there was insufficient information to determine whether or not the reported events were consistent with the disease or due to Strensiq, ophthalmology examinations and renal ultrasounds are recommended at baseline and periodically during treatment to monitor for signs and symptoms of ectopic calcifications and for changes in vision or renal function.

REFERENCES

1. Strensiq prescribing information. Alexion. June 2020.
2. Cohen A, Drake MT. UpToDate Epidemiology and etiology of osteomalacia. Last updated July 2021.
3. Mornet, E. Hypophosphatasia. Orphanet J Rare Dis. 2007;2:40
4. National Organization for Rare Disorders (NORD). Hypophosphatasia. https://rarediseases.org/rare-diseases/hypophosphatasia/
5. National Institute for Health and Care Excellence (NICE). Asfotase alfa for treating paediatric-onset hypophosphatasia. Published date: 02 august 2017.
6. Kishnai PS, Rush ET, Arundel P, et al. Monitoring guidance for patients with hypophosphatasia treated with asfotase alfa. Molecular Genetics and Metabolism 122 (2017) 4-17.

Strensiq (asfotase alfa) Prior Authorization

TARGET AGENT
Strensiq® (asfotase alfa)

Brand (generic)	GPI	Multisource code
18 mg/0.45 mL injection	30905610002020	M, N, O, Y
28 mg/0.7 mL injection	30905610002030	M, N, O, Y
40 mg/1 mL injection	30905610002040	M, N, O, Y
80 mg/0.8 mL injection	30905610002050	M, N, O, Y

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target agent will be approved when ALL of the following are met:

1. The patient has a diagnosis of either perinatal/infantile- OR juvenile-onset hypophosphatasia (HPP) AND ALL of the following:
    A. The patient was < 18 years of age at onset
    AND
    B. The patient is experiencing active disease (e.g., bone pain, fractures, gait problems)
    AND
    C. The patient has/had clinical manifestations consistent with hypophosphatasia at the age of onset prior to age 18 (e.g., vitamin B6-dependent seizures, fractures, lost teeth with roots, skeletal abnormalities: such as rachitic chest deformity leading to respiratory problems or bowed arms/legs, "failure to thrive")
    AND
    D. The patient has/had radiographic imaging to support the diagnosis of hypophosphatasia at the age of onset prior to age 18 (e.g., infantile rickets, alveolar bone loss, craniosynostosis)
    AND
    E. Molecular genetic test has been completed confirming mutations in the *ALPL* gene that encodes the tissue nonspecific isoenzyme of ALP (TNSALP)
    AND
    F. Reduced activity of unfractionated serum alkaline phosphatase (ALP) in the absence of bisphosphonate therapy (i.e., below the normal lab reference range for age and sex)
    AND
    G. ONE of the following:
        i. Elevated serum concentration of pyridoxal 5'-phosphate (PLP) in the absence of vitamin supplements within one week prior to the test
        OR
        ii. Elevated urine concentration of phosphoethanolamine (PEA)
        OR
        iii. Elevated urinary inorganic pyrophosphate (PPi)

    AND
2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
    AND

3. The patient has had an ophthalmology examination and renal ultrasound at baseline (i.e., prior to starting therapy with the requested agent)
   AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication based on the patient's weight

Length of Approval: 6 months

Renewal Evaluation
Target agent will be approved when ALL the following are met:
1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process
   AND
2. There is information supporting that the patient has had a decrease from baseline in at least ONE of the following:
   A. Serum concentration of pyridoxal 5'-phosphate (PLP) in the absence of vitamin supplements within one week prior to the test
      OR
   B. Urine concentration of phosphoethanolamine (PEA)
      OR
   C. Urinary inorganic pyrophosphate (PPi)
   AND
3. There is information supporting that the patient has had clinical improvement from baseline in at least ONE of the following:
   A. Respiratory status
      OR
   B. Growth
      OR
   C. Radiographic findings
   AND
4. There is information supporting that the patient continues to have clinical benefit with the requested agent
   AND
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
6. The patient has been monitored for signs and symptoms of ophthalmic and renal calcifications and for changes in vision or renal function
   AND
7. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
8. The requested quantity (dose) is within FDA labeled dosing for the requested indication based on the patient's weight

Length of Approval: 12 months