Drug Coverage Policy

Effective Date..... 11/1/2024
Coverage Policy Number IP0308
Policy Title..... Strensiq

Enzyme Replacement Therapy – Strensiq

- Strensiq® (asfotase alfa subcutaneous injection – Alexion)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW
Strensiq, a tissue non-specific alkaline phosphatase (TNSALP), is indicated for the treatment of patients with **perinatal/infantile- and juvenile-onset hypophosphatasia** (HPP).[1] Strensiq is an enzyme replacement therapy which replaces human TNSALP.

Disease Overview

HPP is an inherited metabolic disease caused by a loss-of-function pathogenic variant in the gene which codes for TNSALP.[2] TNSALP is tissue-bound and expressed in high concentrations in the liver, kidney, neurons, neutrophils, bone, and teeth.[2,3] In HPP, inorganic pyrophosphate and pyridoxal 5'-phosphate, substrates for TNSALP, are increased and lead to disease manifestations. Inorganic pyrophosphate is an inhibitor of bone mineralization, and its accumulation leads to rickets and osteomalacia. Pyridoxal 5'-phosphate, a derivative of vitamin B_6, is necessary for the synthesis of gamma aminobutyric acid (GABA). However, for pyridoxal 5'-phosphate to enter the neuron, it must be dephosphorylated to allow pyridoxal to enter the neuron where it is rephosphorylated. The decreased synthesis of GABA in HPP leads to seizures.

HPP is a rare disease, with an estimated live-birth incidence, for the severe forms of HPP, of 1:100,000 in Canada and approximately 1:300,000 in Europe.[2,4] Prevalence in certain populations, such as Canadian Mennonites, may be as high as 1:2,500 births. Disease severity can range from neonatal death with almost no skeletal mineralization to dental problems in adults without any bone symptoms.[2-4] In patients most severely affected by HPP, mortality ranges from 50% to nearly 100% during infancy.[2]

Medical Necessity Criteria

Strensiq is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Hypophosphatasia – Perinatal/Infantile- and Juvenile-Onset.** Approve for 1 year if the patient meets ALL the following (A, B, C, and D):
   - **A)** Diagnosis is supported by ONE of the following (i, ii, or iii):
     - **i.** Molecular genetic testing documenting pathogenic tissue non-specific alkaline phosphatase (*ALPL*) gene variants; OR
     - **ii.** Low baseline serum alkaline phosphatase activity; OR
     - **iii.** An elevated level of a tissue non-specific alkaline phosphatase substrate (i.e., serum pyridoxal 5'-phosphate, serum, or urinary inorganic pyrophosphate, urinary phosphoethanolamine); AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient currently has, or has a history of, clinical manifestations consistent with hypophosphatasia; OR
       Note: Examples of clinical manifestations include skeletal abnormalities, premature tooth loss, muscle weakness, poor feeding, failure to thrive, respiratory problems, vitamin B_6-dependent seizures.
     - **ii.** Patient has a family history (parent or sibling) of hypophosphatasia without current clinical manifestations of hypophosphatasia; AND
   - **C)** Disease onset $\leq$ 18 years of age; AND
   - **D)** Strensiq is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of hypophosphatasia or related disorders.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics

References

1. Strensiq® subcutaneous injection [prescribing information]. Cheshire, CT: Alexion; July 2024.
2. Whyte MP. Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges. *J Bone Miner Res*. 2017; 32:667-675.
3. Orima H. Pathophysiology of Hypophosphatasia and the Potential Role of Asfotase Alfa. *Ther Clin Risk Manag*. 2016; 12:777-786.
4. Millan JL, Plotkin H. Hypophosphatasia – Pathophysiology and Treatment. *Actual Osteol*. 2012; 8:164-182.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** coverage policy title from "Asfotase alfa" to "Enzyme Replacement Therapy - Strensiq" **Hypophosphatasia – Perinatal/Infantile- and Juvenile-Onset:** **Added** criterion "an elevated level of a tissue non-specific alkaline phosphatase substrate (i.e., serum pyridoxal 5'-phosphate, serum, or urinary inorganic pyrophosphate, urinary phosphoethanolamine)" for diagnosis of perinatal/infantile-onset or juvenile-onset hypophosphatasia (HPP). For diagnosis by genetic testing, rephrased the term "mutation" to "pathogenic variant".	11/1/2024

The policy effective date is in force until updated or retired.