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Policy Number: C9425-A

Strensiq (asfotase alfa)

PRODUCTS AFFECTED

Strensiq (asfotase alfa)

COVERAGE POLICY

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

This 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 Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:

Perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)

REQUIRED MEDICAL INFORMATION:

This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. PERINATAL/INFANTILE–ONSET HYPOPHOSPHATASIA AND JUVENILE– ONSET HYPOPHOSPHATASIA:

1. Diagnosis of Perinatal (onset before birth)/Infantile-onset hypophosphatasia (HPP) or Juvenile-onset hypophosphatasia (HPP)
AND
2. Documentation of Tissue Non-Specific Alkaline Phosphatase (TNSALP) substrate level

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ELEVATION, indicated by at least ONE (1) of the following [DOCUMENTATION REQUIRED]:

Note: Some labs are interpreted based on the gender- and age-specific reference range determined by each reference laboratory

(a) Serum alkaline phosphatase (ALP) activity/level: LOW

OR

(b) Serum pyridoxal 5'-phosphate (PLP) level: Elevated (above the upper limit of normal at baseline) AND member has not received vitamin B6 (Pyridoxine; Pyridoxal 5'-Phosphate) supplementation in the previous week

OR

(c) Serum or urine phosphoethanolamine (PEA) level: ELEVATED

OR

(d) Urine inorganic pyrophosphate (PPi) level: ELEVATED

AND

3. Provider attests to radiographic evidence of HPP confirmed by: Osteopenia, osteoporosis, or low bone mineral content for age detected by dual-energy x-ray absorptiometry (DEXA)

AND

4. FOR ADULTS ONLY (>18 YEARS OF AGE): Clinical documentation or documented history of at least TWO skeletal and/or dental manifestations indicative of hypophosphatasia including: Rickets, Osteomalacia, Rachitic deformities (rachitic chest, bowed legs, knock-knees), Craniosynostosis (premature closure of skull bones), Delay in skeletal growth resulting in delay of motor development, History of vitamin B6 dependent seizures, Nephrocalcinosis or history of elevated serum calcium, History or presence of non-traumatic postnatal fracture and delayed fracture healing, dental manifestations (i.e. premature loss of primary teeth prior to 5 years of age, defective mineralization of bone and/or teeth)

AND

5. Prescriber attests that history of onset of signs/symptoms of HPP occurred BEFORE 18 years of age [NOTE: Adult-onset (onset at 18 years or older) do NOT meet criteria. Perinatal/infantile onset of signs/symptoms before 6 months of age. Juvenile onset of signs/symptoms between 6 months and 18 years of age.]

AND

6. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal (e.g., ventilator status, radiographic status, height and weight [i.e., Z-score], gait and mobility [e.g., 6MWT])

CONTINUATION OF THERAPY:

A. HYPOPHOSPHATASIA:

1. Documentation that member has responded to treatment with Strensiq (asfotase alfa) as evidenced by objective stability and/or continued disease improvement in clinical signs and/or symptoms of hypophosphatasia as compared to baseline (e.g., ventilator status, radiographic status, height and weight [i.e., Z-score], gait and mobility [e.g., 6MWT]) [DOCUMENTATION REQUIRED]

AND

2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of treatment: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified endocrinologist, geneticist, metabolic specialist, bone and mineral specialist, or physician specialist experienced in the treatment of metabolic bone disorders. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

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AGE RESTRICTIONS:

None

QUANTITY:

Juvenile-onset HPP: maximum 6 mg/kg/week subcutaneously

Perinatal/infantile-onset HPP: maximum 9 mg/kg/week subcutaneously

NOTE: 6 times per week regimen may NOT be authorized; 2 mg/kg 3 times per week dosing only*

*The FDA-approved labeling allows for Strensiq to be injected three times per week or six times per week. Strensiq is covered as a three times per week injection.

Maximum Quantity Limits – 3 mg/kg 3 times per week

PLACE OF ADMINISTRATION:

The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Subcutaneous

DRUG CLASS:

Hypophosphatasia (HPP) Agents

FDA-APPROVED USES:

Indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:

Appendix 1: Clinical Features of Hypophosphatasia by Type

Several clinical forms of hypophosphatasia (HPP) are currently recognized:⁶

Perinatal HPP (onset before or at birth) is the most pernicious form, resulting in a high percent of stillborn births. Newborns that survive birth have an estimated mortality of about 50% in the first year of life with many complications including respiratory failure due to rachitic chest disease and hypoplastic lungs.

Childhood HPP (also referred as childhood onset; onset between 6 months and 18 years) has variable symptoms; however, premature loss of primary teeth before the age of five is classical feature of HPP. Children may present with delayed mobility, waddling gait, delayed growth, frequent fractures, and osteopenia.

Adult HPP (onset at 18 years or older) can be associated with rickets or early loss of adult teeth. Adults may also suffer from pain due to osteomalacia, fracture, pseudogout, and calcific peri-arthritis.

Odontohypophosphatasia (only dental clinical symptoms): The mildest form of the condition, called odontohypophosphatasia, only affects the teeth.¹ The milder forms, especially adult forms and odontohypophosphatasia, may be inherited in an autosomal recessive or autosomal dominant

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manner.

| Type | Inheritance | Cardinal Features | Dental Features | Clinical Diagnosis |
|------------------------|-------------|---|--|---|
| Perinatal (severe) | AR | Hypomineralization, osteochondral spurs | ± ¹ | Radiographs, prenatal ultrasound examination |
| Perinatal (benign) | AR or AD | Long-bone bowing, benign postnatal course | ± | Prenatal ultrasound examination, clinical course |
| Infantile ² | Mostly AR | Craniosynostosis, Hypomineralization, rachitic ribs, hypercalciuria | Premature loss, deciduous teeth | Clinical course, radiographs, laboratory findings |
| Childhood (juvenile) | AR or AD | Short stature, skeletal deformity, bone pain/fractures | Premature loss, deciduous teeth (incisors) | Clinical course, radiographs, laboratory findings |
| Adult ³ | AR or AD | Stress fractures: metatarsal, tibia; chondrocalcinosis | ± | Clinical course, radiographs, laboratory findings |

| Type | Inheritance | Cardinal Features | Dental Features | Clinical Diagnosis |
|-------------------------------|-------------|--------------------|---------------------------------------|--|
| <u>Odontohypophosphatasia</u> | AR or AD | Alveolar bone loss | Exfoliation (incisors), dental caries | Clinical course, dental panorex, laboratory findings |

Key: AR = [autosomal recessive](#); AD = [autosomal dominant](#)

- ¹ In the past individuals with severe phenotypes have typically died before teeth erupted and could be lost. In the new "treated perinatal (severe) and infantile" category, the dental features are not precisely known but emerging data suggests the possibility of such features.
- ² Rare reported cases of infantile hypophosphatasia that have normal serum alkaline phosphatase activity (in vitro) have been designated "pseudohypophosphatasia." The biochemical and molecular basis of pseudohypophosphatasia remains unclear.
- ³ Persons with adult hypophosphatasia may give a history of features typically reported in childhood (juvenile), infantile, and even prenatal hypophosphatasia.

Appendix 2: Weight-Based Dosing for Administration of 2 mg/kg Three Times per Week

| Guidance for 2 mg/kg subQ 3 Times Weekly Dosage Option | | | |
|--|------------------------|-----------------------|---------------------|
| Weight (kg) | Weight-based dose (mg) | Injection volume (mL) | Vial size(s) to use |

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| | | | |
|----|-----|------|------------------|
| 3 | 6 | 0.15 | 18 mg/0.45 mL |
| 4 | 8 | 0.2 | 18 mg/0.45 mL |
| 5 | 10 | 0.25 | 18 mg/0.45 mL |
| 6 | 12 | 0.3 | 18 mg/0.45 mL |
| 7 | 14 | 0.35 | 18 mg/0.45 mL |
| 8 | 16 | 0.4 | 18 mg/0.45 mL |
| 9 | 18 | 0.45 | 18 mg/0.45 mL |
| 10 | 20 | 0.5 | 28 mg/0.7 mL |
| 15 | 30 | 0.75 | 40 mg/mL |
| 20 | 40 | 1 | 40 mg/mL |
| 25 | 50 | 1.25 | 2 x 28 mg/0.7 mL |
| 30 | 60 | 1.5 | 2 x 40 mg/mL |
| 35 | 70 | 1.75 | 2 x 40 mg/mL |
| 40 | 80 | 0.8 | 80 mg/0.8 mL |
| 50 | 100 | 1 | 2 x 80 mg/0.8 mL |
| 60 | 120 | 1.2 | 2 x 80 mg/0.8 mL |
| 70 | 140 | 1.4 | 2 x 80 mg/0.8 mL |
| 80 | 160 | 1.6 | 2 x 80 mg/0.8 mL |

Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Hypophosphatasia (HPP) is a rare autosomally inherited metabolic bone disorder, with a range of bone development–related symptoms whose severities depend on the patient’s age at disorder onset. HPP is caused by various mutations to the alkaline phosphatase, liver/bone/kidney (ALPL) gene; these mutations result in abnormally low systemic levels of alkaline phosphatase, a key bone mineralization enzyme. HPP affects the development of bones and teeth and the condition disrupts the mineralization process, in which minerals such as calcium and phosphorus are in developing bones and teeth.

HPP symptoms vary depending on severity and age at initial presentation. The signs and symptoms of hypophosphatasia vary widely and can appear anytime from before birth to adulthood. Generally, the earlier the presentation, the more severe the disease.

Signs and symptoms include rickets, softening and weakening of the bones (osteomalacia), bone deformity and a greater incidence of fractures. Hypophosphatasia can also lead to chronic debilitating pain, muscle weakness, generalized seizures due to vitamin B6 deficiency, as well as renal and respiratory complications.

Although adult-onset HPP has relatively mild symptoms such as premature tooth loss, infant- and juvenile-onset HPP are marked by more severe symptoms including cranial hypo mineralization, pneumonia, and abnormal bone development. Early-onset HPP forms have mortality rates as high as 50%.

There are no guidelines for the treatment of hypophosphatasia. Management recommendations have focused on supportive care and trying to limit sign/symptom sequelae. Recommendations include vitamin B6 supplementation in patients with seizures, NSAIDs for pain, surgery for individuals with intracranial

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pressure and/or to repair bone fractures, and regular dental visits to preserve primary dentition.

Clinical trials have tested teriparatide, bone marrow transplantation, and other procedures such as transplantation therapy using bone fragments and cultured osteoblasts, as well as enzyme replacement therapies (i.e., asfotase alfa).^{4,6}

Enzyme replacement therapy (ERT). Autosomal recessive hypophosphatasia remains an extremely rare and severe condition.

Strensiq (asfotase alfa) is the first therapy approved in the United States for the treatment of patients with perinatal, infantile and juvenile-onset hypophosphatasia (HPP). Strensiq is a recombinant TNSALP fusion protein intended as an enzyme replacement therapy. It is administered via subcutaneous injection 3 or 6 times per week with weight-based dosing. Strensiq was studied in 4 prospective open-label trials conducted in 99 patients with perinatal/infantile- and juvenile-onset hypophosphatasia.^a The treatment duration and long-term effects of ERT with asfotase alfa remain unknown for perinatal and infantile HPP. Clinical trials are in Phase IV, with patients treated up to 78 months at the time of FDA approval.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Strensiq (asfotase alfa) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Strensiq (asfotase alfa) include: No labeled contraindications.

Hypersensitivity reactions, including anaphylaxis, have been reported; symptoms consistent with anaphylaxis, including difficulty breathing, choking sensation, nausea, periorbital edema, and dizziness, have been reported. Reactions may occur within minutes after administration or in patients on treatment for more 1 year. Other hypersensitivity reactions (e.g., vomiting, fever, headache, flushing, irritability, chills, skin erythema, rash, pruritus, oral hypoesthesia) have also been reported.

If a severe hypersensitivity reaction occurs, discontinue treatment and initiate appropriate medical treatment. If the decision is made to re-administer, monitor patients for a reoccurrence of signs and symptoms of a severe hypersensitivity reaction

OTHER SPECIAL CONSIDERATIONS:

Antibody formation: The presence of antibodies has been reported in 78% of treated patients in clinical trials. Approximately 45% of these patients showed the presence of neutralizing antibodies. Formation of antidrug antibody results in a reduced systemic exposure of asfotase alfa.

Do not use the 80 mg per 0.8 mL vial in pediatric patients weighing < 40 kg (systemic exposure of asfotase alfa achieved with the 80 mg per 0.8 mL vial [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.

CODING/BILLING INFORMATION

Note: 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

| HCP CS CODE | DESCRIPTION |
|-------------|-------------|
| NA | |

AVAILABLE DOSAGE FORMS:

Strensiq SOLN 18MG/0.45ML single-dose vial

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Strensiq SOLN 28MG/0.7ML single-dose vial

Strensiq SOLN 40MG/ML single-dose vial

Strensiq SOLN 80MG/0.8ML single-dose vial

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| SUMMARY OF REVIEW/REVISIONS | DATE |
|---|----------------------------|
| REVISION- Notable revisions: Required Medical Information Continuation of Therapy Age Restrictions Available Dosage forms References | Q3 2023 |
| REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/Discontinuation References | Q3 2022 |
| Q2 2022 Established tracking in new format | Historical changes on file |