Original Effective Date: 06/01/2016
Current Effective Date: 10/09/2024
Last P&T Approval/Version: 07/31/2024
Next Review Due By: 07/2025
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. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

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

1. Documented 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 ELEVATION, indicated by at least ONE 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 (PEP) 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]

AGE RESTRICTIONS:
None

QUANTITY:
Juvenile-onset HPP: Maximum 6 mg/kg/week subcutaneously (see Appendix 2)
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 – 2-3 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:[G]

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 periarthritis.

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

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
Odontohypophosphatasia	AR or AD	Alveolar bone loss	Exfoliation (incisors), dental caries	Clinical course, dental panorex, laboratory findings

Key:AR = autosomalrecessive; AD = autosomaldominant

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 pseudohypophosphasia 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

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 as50%.

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

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.

OTHER SPECIAL CONSIDERATIONS:

Strensiq (asfotase alfa) has a Black Box Warning for hypersensitivity reactions including anaphylaxis. Patients treated with enzyme replacement therapies have experienced life threatening hypersensitivity reactions, including anaphylaxis. Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. Initiate STRENSIQ under the supervision of a healthcare provider with appropriate medical monitoring and support measures. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue STRENSIQ and immediately initiate appropriate medical treatment, including use of epinephrine. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur.

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

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

Strensiq SOLN 18MG/0.45ML single-dose vial
Strensiq SOLN 28MG/0.7ML single-dose vial
Strensiq SOLN 40MG/ML single-dose vial
Strensiq SOLN 80MG/0.8ML single-dose vial

REFERENCES

1. Strensiq (asfotase alfa) [prescribing information]. Cheshite, CT. Alexion Pharmaceuticals, Inc. July 2024.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited2016-01-27]. Available from: http://clinicaltrials.gov/.
3. FDA [Online Press Release]. FDA approves new treatment for rare metabolic disorder. FDA News Release. Silver Spring, MD: FDA; October 23, 2015.
4. Strensiq (asfotase alfa) CEDR Medical Review. FDA/CEDR resources page. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125513Orig1s000MedR.p df
5. Mornet E, Nunes ME. Hypophosphatasia. Gene Reviews [Internet]. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1150 Updated February 4, 2016. Accessed May 2020
6. Rockman-Greenberg C. Hypophosphatasia. Pediatric Endocrinol Rev. 2013;10(suppl2):380- 388.
7. Mornet E, Nunes ME. Hypophosphatasia. Orphanet J Rare Dis. 2007;2:40.
8. Alexion Pharmaceuticals. Current patient management recommendations. Available at: http://hypophosphatasia.com/hcp/management-strategies. Updated 2014. Accessed June 2016.
9. National Organization for Rare Disorders (NORD). Hypophosphatasia. Nord Guide to Rare Disease Database. Published 2017. Available at: https://rarediseases.org/rare- diseases/hypophosphatasia/. Accessed July 25, 2019.
10. Hofmann C, Rockman-Greenberg C, Harmatz P, Moseley S, Odrljin T, Liese J. Improvement in bone manifestations and respiratory status in infants and young children with HPP treated with asfotase alfa: an update on the ENB-010-10 trial [abstract]. Bone Abstracts.2015;4:abstract OC18.
11. National Institute of Health. Genetic and Rare Disease Information Center:Hypophosphatasia. URL: https://rarediseases.info.nih
12. United States National Library of Medicine. Genetics Home Reference: Hypophosphatasia. September 2007. URL: http://ghr.nlm.nih.gov/condition=hypophosphatasia. Available from internet.
13. Beck C., Morbach H., Stenzel M., Colmann H., Schneider P., and Girschick HJ. Hypophosphatasia-Recent Advances in Diagnosis and Treatment. The Open bone Journal, 2009; I:8-15. Available at: http://benthamopen.com/contents/pdf/TOBONEJ/TOBONEJ-1- 8.pdf
14. National Institute for Health and Care Excellence (NICE). The draft guidance on asfotase alfa available on the NICE website from 27 November 2015.
15. Choida, V., & Bubbear, J. S. (2019). Update on the management of hypophosphatasia. Therapeutic Advances in Musculoskeletal Disease, 11, 1759720X1986399. https://doi.org/10.1177/1759720x19863997

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Contraindications/Exclusions/ Discontinuation Other Special Considerations References	Q3 2024
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