| Policy and Procedure | |
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| **PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCEND043.0425** | **ENDOCRINE AND METABOLIC DRUGS**<br>**STRENSIQ®**<br>(asfotase alfa for subcutaneous injection) |
| **Effective Date: 6/1/2025** | **Review/Revised Date**: 03/16, 05/16,03/17, 03/18, 03/19, 03/20, 02/21, 02/22, 02/23. 02/24, 06/24, 02/25 (snm) |
| **Original Effective Date: 06/16** | **P&T Committee Meeting Date**: 04/16, 05/16, 04/17, 04/18, 04/19, 04/20, 04/21, 04/22, 04/23, 04/24, 08/24, 04/24 |
| **Approved by: Oregon Region Pharmacy and Therapeutics Committee** | |

**SCOPE:**
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

**APPLIES TO:**
Commercial
Medicaid

## POLICY CRITERIA:

**COVERED USES:**
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

**REQUIRED MEDICAL INFORMATION:**
Initial authorization requires all the following criteria to be met:

1. Diagnosis of perinatal/infantile or juvenile-onset hypophosphatasia (HPP) and all of the following:
    a. One of the following:
        i. Molecular genetic test has been completed confirming mutations in the ALPL gene that encodes the tissue nonspecific isoenzyme of ALP (TNSALP)
        OR
        ii. Total serum alkaline phosphatase (ALP) below the lower limit of normal for age *AND* Plasma pyridoxal-5'-phosphate (PLP) above the upper limit. Note: Plasma PLP should not be measured while the member is receiving pyridoxine treatment
    b. Onset of clinical manifestations (See Appendix 1 for HPP related clinical signs and symptoms) OR radiographic imaging (See Appendix 2 for radiographic features that support a diagnosis of HPP) consistent with hypophosphatasia prior to the age of 18 years
2. Dosing is within the Food and Drug Administration approved label dose

**Reauthorization:**

1. Response to therapy supporting clinical improvement from baseline (prior to starting therapy with the requested agent) or stabilization of condition in at least ONE of the following:
    a. Respiratory status OR
    b. Growth OR
    c. Radiographic findings
2. Dosing is within the Food and Drug Administration approved label dose

**EXCLUSION CRITERIA:**
Adult-onset hypophosphatasia or odonto-hypophosphatasia

**AGE RESTRICTIONS:** N/A

**PRESCRIBER RESTRICTIONS:**
Initial and reauthorization must be prescribed by or in consultation with a specialist in the area of perinatal/infantile or juvenile-onset hypophosphatasia (such as endocrinologist, geneticist)

**COVERAGE DURATION:**
Initial authorization will be approved for six months. Reauthorization will be approved for 12 months.

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*Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.*

*Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.*

*Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.*

*Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.*

**INTRODUCTION:**
Asfotase alfa is a tissue nonspecific alkaline phosphatase indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP). HPP is caused by a deficiency in tissue-nonspecific alkaline phosphatase (TNSALP) enzyme activity, which leads to elevations in several TNSALP substrates, including

inorganic pyrophosphate (PPi). Elevated extracellular levels of PPi, block hydroxyapatite crystal growth which inhibits bone mineralization and causes an accumulation of un-mineralized bone matrix. This manifests as rickets and bone deformation in infants and children, and as osteomalacia (softening of bones) once growth plates close, along with muscle weakness. Replacement of the TNSALP enzyme upon asfotase alfa treatment reduces the enzyme substrate levels. Asfotase alfa is currently only FDA approved for perinatal/infantile- and juvenile-onset HPP and is not currently indicated for adult onset or odonto-HPP.

**FDA APPROVED INDICATIONS:**

- Treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia

**POSITION STATEMENT:**

- HPP is a genetic, chronic, progressive, and life-threatening ultra-rare metabolic disease characterized by low alkaline phosphatase (ALP) activity and defective bone mineralization. Defective mineralization results in bones that are soft and prone to fracture and deformity. Defective mineralization of teeth can lead to premature tooth loss.
- There are several forms of HPP, including perinatal severe HPP, infantile HPP (onset < six months of age), childhood HPP (onset < months to 18 years of age), adult HPP (onset <18 years of age) and odonto-HPP (least severe form HPP). HPP can cause destruction and deformity of bones and other skeletal abnormalities, as well as systemic complications such as profound muscle weakness, seizures, pain, and respiratory failure, which can lead to premature death in infants.
- The perinatal and infantile forms are the most severe and life-threatening forms with mortality rates as high as 100% in the perinatal form and 50% in the infantile-onset form. It is estimated that the prevalence of severe HPP in the general population is 1:100,000.
- The FDA approval of asfotase alfa was based on four prospective, open-label studies and supporting extension trials comprising of patients with perinatal-, infantile and juvenile-onset HPP.[1]
    - Given the rarity and life-threatening nature of the disease the clinical trials were relatively small and were of a non-comparative design (data was compared to historical cohorts). However, the studies demonstrate the potential benefit of asfotase alfa for the treatment of HPP.
    - Relative to historical control cohorts, survival and ventilation-free survival were significantly prolonged in asfotase alfa-treated patients under the age of five, due to improvements in bone mineralization.

- Bone mineralization was also shown to improve in adolescent patients with infantile and juvenile-onset HPP and those patients showed improvements in mobility and growth compared to historical cohorts.

**Evidence for Use in the Adult Population:**

- Asfotase alfa is FDA approved for perinatal/infantile- and juvenile-onset HPP and is not approved for adult onset or odonto-HPP. It was granted Breakthrough Therapy Designation (BTD) for perinatal-, infantile- and juvenile-onset HPP. However, per the FDA BTD was not granted for adult-onset HPP due to insufficient clinical evidence.
- The majority of patients in the approval trials were pediatric patients one day to 16 years of age (89/99 [90%]). The only formally published trials that are currently available are for perinatal/infantile HPP.
- The data available for the use of Strensiq® in the adult population is limited. The information summarized is based in the package insert and data included in the application submitted to the FDA.
- Study ENB-009-10[7]
  - Multicenter, randomized, open-label, dose-ranging, concurrent control pilot study.
  - Overall objectives were to evaluate the safety, efficacy, and pharmacokinetics (PK) of asfotase alfa in adolescents and adults with HPP. The primary endpoints were change from baseline in PPi and PLP.
  - Study enrolled 19 adolescent (>12 y/o) and adult patients with HPP, regardless of age at onset. Of the patients enrolled 13 were adults and six were adolescents. However, only the patients with perinatal/infantile- and juvenile-onset HPP were included from this study. Three of the adult patients' data was not included in the final approval because they had adult onset HPP or the age of onset was unknown.
  - The change in PPi in the two control groups from baseline to Month six compared to the control group was not statistically significant (p=0.0715) but the control group did demonstrate a greater mean change.
  - For the change in plasma PLP the difference between the asfotase alfa combined treatment group and the control group was statistically significant (p=0.0285).
  - At baseline, most adolescent and adult patients had increased osteoid and prolonged mineralization lag time consistent with osteomalacia. Following treatment, median change in osteoid thickness and volume % were similar between treatment and control groups. The FDA reviewer commented that unlike the biopsy results from children with HPP from other studies the results from Study ENB-009-10 do not support the efficacy of asfotase alfa in treating osteomalacia. However, once again it was noted that study doses were lower than the FDA approved marketed dose. DEXA scans were also taken but these test results were confounded by the presence of

fracture fixation hardware in many patients. The DEXA scans for the adult patients were not presented but it was noted that the adult patients only had small increases in hip and spine scores. The following conclusion about this study was also supplied "Compared to younger children, the number of treated adolescents is smaller, and the bone related data less consistent: paired biopsies in two treated adolescents did not show improvement in osteomalacia, and radiographic indices in six adolescents showed minimal positive changes during treatment, less than in younger children. Biopsies in adults (who mostly had juvenile onset HPP) also showed no clear evidence of improvement. The adolescent/adult study used small, possibly suboptimal doses. Thus, it is uncertain whether there is significant skeletal benefit (reduced osteomalacia and fracture risk) to patients from continuing (or initiating) treatment with asfotase alfa beyond epiphyseal closure".

- ENB-001-08[9] is another study that looked at asfotase alfa in adult patients.
    - A 1-month, open-label, dose escalation phase 1 trial in adult patients with HPP.
    - This phase 1 trial enrolled adult patients with HPP based on current age and not age of disease onset. Some adult patients in this trial may have juvenile-onset disease and remain symptomatic as adults.
    - Six patients enrolled and completed the study. The patient age range was 24 to 58 years old. Four of these patients were allowed to enroll in Study ENB-009-10.
    - Patients were treated at Week one with a single intravenous (IV) dose of asfotase alfa followed by weekly SC injections for weeks two through four. The first cohort of patients (n=3) received asfotase alfa 3 mg/kg IV followed by weekly SC doses of 1 mg/kg. The second cohort (n=3) received asfotase alfa 3 mg/kg IV followed by weekly SC doses of 2 mg/kg/week.
    - Full results data was not provided but it was reported that asfotase alfa was safe and well tolerated, and the trial demonstrated a dose-dependent treatment effect and an overall decreasing trend in biomarkers (PPi and PLP).
    - There were no consistent changes in bone mineral density, pain, or bone imaging but this may have been due to the short length of the trial.
- Given the limited data in adults and high cost of therapy, asfotase alfa will only be considered medically necessary for adult patients that have confirmed clinical onset of disease prior to 18 and have severe manifestations of the disease.

**REFERENCE/RESOURCES**:

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Pharmaceuticals, Inc. July 2024.
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14. National Center for Advancing Translational Sciences. Hypophosphatasia. Last updated January 2025. Available at: https://rarediseases.info.nih.gov/diseases/6734/hypophosphatasia Accessed February 24, 2025.

**Appendix 1**[13,14]: Examples of clinical signs and symptoms of HPP

- Vitamin B6-dependent seizures
- Respiratory insufficiency
- Hypotonia, myopathy, gross motor delay,
- Low trauma or non-traumatic fractures
- Premature loss of deciduous teeth, carious teeth, or abnormal dentition,
- Gait disturbance such as delayed walking or waddling gait,
- Osteopenia, osteoporosis, or low bone mineral content for age attributable to hypophosphatasia,
- Hypercalcemia, hypercalciuria, nephrocalcinosis

**Appendix 2**[13,14]: Examples of radiographic features supporting diagnosis of HPP

- Knock knees
- Bowing of leg(s)
- Rachitic chest
- Craniosynostosis
- Infantile rickets
- Osteochondral spurs

**Appendix 3:** FDA approved dosing. The safety and efficacy of higher doses has not been established and is considered investigational

| Drug name | Indication | Dosing schedule | Availability (Vials) |
| --- | --- | --- | --- |
| asfotase alfa (Strensiq) | Perinatal/infantile- and juvenile-onset hypophosphatasia (HPP) | 2 mg/kg subcutaneously three times a week or 1 mg/kg six times a week (for Perinatal/infantile-onset disease ONLY: a total of 9mg/kg weekly may be needed) | 18mg/0.45ml, 28mg/0.7ml, 40mg/ml, 80mg/0.8ml |

**Appendix 4: Reference ALP Serum levels**[10]

| Age | Male (IU/L) | Female (IU/L) |
| --- | --- | --- |
| 0 to 5 d | 47−127 | 47−127 |
| 6 to 10 d | 29−242 | 29−242 |
| 11 to 20 d | 109−357 | 109−357 |
| 21 to 30 d | 94–494 | 94–494 |
| 1 to 2 m | 149−539 | 149−539 |

| | | |
| --- | --- | --- |
| 3 to 6 m | 131−452 | 131−452 |
| 7 to 11 m | 117−401 | 117−401 |
| 12 m to 6 y | 158−369 | 158−369 |
| 7 to 12 y | 150−409 | 150−409 |
| 13 y | 156−435 | 78−227 |
| 14 y | 114−375 | 64−161 |
| 15 y | 88−279 | 56−134 |
| 16 y | 74−207 | 51−121 |
| 17 y | 63−161 | 47−113 |
| 18 to 20 y | 51−125 | 42−106 |
| >20 y | 44−121 | 44−121 |