Strensiq®
(asfotase alfa) for injection | 40 mg/mL

Sample Letter of Medical Necessity for STRENSIQ® (asfotase alfa)

For perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)

STRENSIQ® (asfotase alfa) INDICATION & SELECT IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING

INDICATION

STRENSIQ® (asfotase alfa) is indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

SELECT IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING

WARNING: 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 *[see Warnings and Precautions (5.1)]*.

Introduction

Payers may request a letter of medical necessity to support coverage of STRENSIQ® (asfotase alfa). The letter should explain why the drug is medically necessary for the specific patient and may include supporting documentation (eg, medical records, peer-reviewed literature, Prescribing Information, clinical treatment history, etc). The letter may be submitted as part of a prior authorization (PA) request, with the claim form, or in response to a payer's request for additional documentation. The letter should include patient-specific information, be on your letterhead, be signed by the prescriber, and be submitted to a payer to support a PA request or claim for STRENSIQ.

This sample letter of medical necessity is provided for informational purposes only and is not based on legal advice or official guidance from payers. It is not intended to increase or maximize reimbursement by any payer. Alexion does not warrant, promise, guarantee, or make any statement that the use of this information will result in coverage or payment for STRENSIQ or that any payment received will cover providers' costs.

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[John Doe, MD]
[Address]
[City, State ZIP Code]
[(888) 555-5555]

SAMPLE ONLY
Please copy onto your letterhead.

[Date]
[Contact Name],
[Title]
[Name of Health Insurance Plan or pharmacy benefit manager (PBM)]
[Address]
[City, State ZIP Code]

Letter of Medical Necessity for STRENSIQ® (asfotase alfa) [Request for Expedited Review Due to Medical Urgency]
Insured: [Name]
Policy Number: [Number]
Group Number: [Number]
Date(s) of service: [Date(s)]

Dear [Contact Name],
I am writing on behalf of my patient, [First Name] [Last Name], to request that [name of health insurance company] approve coverage and appropriate reimbursement associated with [Mr/Ms/Mrs/other title] [Patient's Last Name]'s treatment with STRENSIQ® (asfotase alfa), an enzyme replacement therapy. STRENSIQ is the only therapy approved by the Food and Drug Administration (FDA) that is indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

PATIENT MEDICAL OVERVIEW

[First Name] [Last Name] is a[n] [age]-year-old [gender] born [MM/DD/YYYY] who requires treatment with STRENSIQ after being diagnosed with [perinatal/infantile- OR juvenile-onset HPP, insert International Classification of Diseases, 10th Revision, Clinical Modification diagnosis]. The patient was diagnosed as of [date of diagnosis MM/DD/YYYY], after first showing onset of HPP symptoms at age [insert age of onset]. [Mr/Ms/Mrs/other title] [Patient's Last Name] has been in my care for HPP since [MM/DD/YYYY].

HPP MEDICAL HISTORY

[Health plans and PBMs may have different requirements. It is important to complete the benefits investigation and understand the key clinical and coverage criteria for each patient's plan. You may contact the patient's health plan or PBM to obtain the coverage policy and confirm documentation requirements prior to submitting any evidence. Please include information from the sections below as appropriate for the patient's specific policy.]

1 Clinical Signs and Symptoms [see page 5 for further details]
[Describe the progression of these signs and symptoms over time, highlighting how the disease has evolved and impacted the patient's health status.]

- Current HPP Signs and Symptoms: [Describe the patient's HPP signs and symptoms, including how they are currently impacting the patient and how they relate to earlier manifestations of the disease.]
- Juvenile-Onset HPP Signs and Symptoms: [Document and describe the signs and symptoms at the age of HPP onset (under 18 years), noting the patient's age and school grade. This information provides important developmental context or milestones.]

[John Doe, MD]
[Address]
[City, State ZIP Code]
[(888) 555-5555]

SAMPLE ONLY

Please copy onto your letterhead.

2 Laboratory Test Results [see page 6 for further details]
[Provide the required laboratory results based on the patient's benefits investigation.]

- Alkaline phosphatase (ALP) activity level: [Coverage policies typically require laboratory confirmation of persistently low age- and sex-adjusted ALP activity levels. Please provide the corresponding laboratory results, including at least 2 recent ALP values taken more than 30 days apart or as required by coverage criteria.]
- ALP substrate level (serum pyridoxal 5′-phosphate [PLP]/vitamin B6 or phosphoethanolamine [PEA]): [Coverage policies almost always require evidence of an elevated substrate. It is important to verify which substrate(s) are required by the patient's specific health plan and include the corresponding laboratory results in this letter.]

[Based on the benefits investigation and your patient's health plan requirements, please ensure that all applicable coverage criteria for the sections below are appropriately addressed.]

3 Radiographic Evidence [see page 6 for further details]
[Some PBMs, payers, or health plans may require radiographic evidence—either current or historical—to confirm skeletal manifestations of HPP.]

4 Genetic Test Results [see page 6 for further details]
[Refer to a patient's health plan to understand if genetic testing is optional or required for the initial authorization or reauthorization for STRENSIQ® (asfotase alfa).]

In my medical opinion, STRENSIQ® (asfotase alfa) is the most appropriate and only FDA-approved treatment for [First Name] [Last Name]'s HPP based on the clinical efficacy and safety data.

TREATMENT PLAN
I have prescribed the following, based on the recommended regimen for HPP in the Prescribing Information for STRENSIQ: [Describe the patient's prescribed dosage and frequency based on the patient's diagnosis, body weight, etc].

SUMMARY
Based on the above facts, I am confident you will agree that STRENSIQ is indicated and medically necessary for this patient. For your convenience, I am enclosing [list enclosures such as supporting clinical documentation, Prescribing Information, FDA approval letter for STRENSIQ in HPP, copy of patient's insurance card, etc].

If you have any further questions, please feel free to call me at [physician's phone number] to discuss.

Thank you in advance for your immediate attention to this request.

Sincerely,
[Physician's Name, Degree Initials]
[Provider Identification Number]
[Physician's Practice Name]
[Physician's Phone Number]
[Physician's Fax Number]
[Physician's Email]

Enclosures [Supporting clinical documentation, Prescribing Information, FDA approval letter for STRENSIQ in HPP, copy of patient's insurance card, etc]

Please copy language above line for sample letter.

Medical History

Please include all relevant documentation supporting a confirmed diagnosis of HPP for the appropriate patient population—STRENSIQ® (asfotase alfa) is indicated for the treatment of patients with perinatal/infantile-onset and juvenile-onset HPP. Documentation should include your patient's clinical presentation, medical history, and applicable laboratory or test results.[1]

1 Clinical Signs and Symptoms

Below are possible clinical signs and symptoms for HPP[a]—it is encouraged to accurately capture the following information in the patient's chart notes: 1) current signs and symptoms and 2) signs and symptoms prior to age 18 per the Prescribing Information. Describe the patient's HPP signs and symptoms, including how they are currently impacting the patient and how they relate to earlier manifestations of the disease.

Skeletal/Orthopedic[2-4]

- Hypomineralization
- Skeletal deformities (eg, enlarged wrist and ankle joints observed in infantile rickets, abnormal skull shape in infants)
- Fractures/pseudofractures (slow to heal)
- Craniosynostosis (in infants)
- Rachitic chest (in infants)
- Rickets (in children)
- Bowed legs or knock knees
- Bone pain
- Osteomalacia

Neurologic[3,4]

- Vitamin B6-responsive seizures (in infants)
- Increased intracranial pressure (in infants)
- Headaches
- Mood changes (anxiety, depression)

Dental[2,4]

- Premature deciduous tooth loss/nontraumatic tooth loss (with root intact)
- Poor/abnormal dentition

Muscular/Rheumatologic[2-4]

- Muscle weakness
- Fatigue
- Hypotonia
- Muscle/joint pain
- Delayed walking
- Waddling gait
- Pseudogout
- Ectopic ossification

Renal[4]

- Hypercalcemia
- Hypercalciuria
- Nephrocalcinosis

Growth/Development (Children)[2,4]

- Failure to thrive
- Delayed/missed motor milestones
- Short stature

Respiratory (Infants)[3-4]

- Respiratory failure
- Respiratory complications (eg, respiratory support)
- Respiratory problems (eg, pneumonia)

a. This list is not exhaustive and all patients may not present in the same way. Treatment may not have an impact on all the signs and symptoms listed and inclusion does not imply efficacy.

Medical History (Cont'd)

2 Laboratory Test Results

Note: Refer to each patient's individual coverage policy to understand which elevated substrate results are required for STRENSIQ® (asfotase alfa) initial authorization or reauthorization.

ALP

Evidence of persistently (defined as at least 2 recent ALP values more than 30 days apart or as specified by coverage criteria) low age- and sex-adjusted ALP activity levels, based on the reference range of the testing laboratory.[2,4,5]

- While reduced ALP activity level below the age- and sex-specific reference range is an essential starting point to consider a diagnosis of HPP, there are scenarios that may contribute to a higher ALP serum activity level result compared to the established lower level of normal reference range. It is also important to understand that ALP activity in serum or plasma does not correlate immediately with clinical disease severity, nor does it accurately reflect actual enzyme function within different tissues.[6,7]

PLP/Vitamin B6 or PEA

Evidence of elevated tissue-nonspecific alkaline phosphatase (TNSALP) substrate levels (eg, PLP/vitamin B6 or PEA) can be found in urine/blood test results.[2,4]

- Major disease biochemical markers of HPP are persistently low age- and sex-adjusted ALP and elevated PLP and PEA levels. However, PLP and PEA levels may differ even among patients with a confirmed diagnosis of HPP.[4,8-10]

For additional information, refer to articles in the "ALP Activity Level: Reference Ranges," "ALP Activity Level: Variability Between Patients," "PLP (Vitamin B6): Reference Ranges," "PLP (Vitamin B6): Variability Among Patients," "PEA: Reference Ranges," and "PEA: Variability Among Patients" sections of the resource A Compendium of Hypophosphatasia (HPP) References for STRENSIQ® (asfotase alfa).

3 Radiographic Evidence

Note: Refer to each patient's individual coverage policy to understand if radiographic evidence is required for STRENSIQ initial authorization or reauthorization.

Radiographic evidence may be required by payers to confirm skeletal manifestations of HPP. Common examples of skeletal manifestations accepted by payers include osteopenia, osteoporosis, or low bone mineral content for age as seen on X-rays, as well as bone fractures or pseudofractures identified through bone density scans.[4,10,11]

In the Absence of Radiographic Imaging:

Adult patients with HPP may present with a heterogeneous range of clinical manifestations, with or without skeletal involvement, irrespective of age at disease onset. Patients with HPP can experience considerable disability and compromised quality of life regardless of whether they have any overt skeletal manifestations.[12,13] In the absence of applicable radiographic imaging, please describe how the nonskeletal manifestations of HPP have affected the patient's physical functioning and activities of daily living.

For additional information, refer to the articles in the "HPP in the Absence of Skeletal Manifestations" section of the resource A Compendium of Hypophosphatasia (HPP) References for STRENSIQ® (asfotase alfa).

4 Genetic Test Results

Note: Refer to each patient's individual coverage policy to understand if genetic testing results are required for STRENSIQ initial authorization or reauthorization.

Although Genetic Testing May Help Support a Diagnosis of HPP, It Is Not Required for Clinical Diagnosis:

If a patient has a negative or variant of unknown significance (VUS) result and you are sending in the test result:
Refer to the articles in the "Genetic Testing and Diagnostic Criteria", "Genetic Testing: Negative Test Result/ Undetectable Mutations", and/or "Genetic Testing: Variant of Unknown Significance" sections of the resource A Compendium of Hypophosphatasia (HPP) References for STRENSIQ® (asfotase alfa) for additional information.

Resources Available to You

- A Compendium of Hypophosphatasia (HPP) References for STRENSIQ® (asfotase alfa) provides information about specific scientific data and publications that may provide additional evidence for your appeal letter.

For additional access and reimbursement resources for STRENSIQ® (asfotase alfa), please visit:

Explore Alexion Access Navigator

ALEXION ACCESS NAVIGATOR

Alexion Access Navigator is a dedicated resource website for US healthcare professionals and their offices that contains downloadable access and reimbursement materials for STRENSIQ® (asfotase alfa).

Online: https://alexionaccessnavigator.com

References: 1. STRENSIQ. Prescribing Information. Alexion Pharmaceuticals, Inc. **2.** Rush E, Brandi ML, Khan A, et al. Proposed diagnostic criteria for the diagnosis of hypophosphatasia in children and adolescents: results from the HPP International Working Group. *Osteoporos Int*. 2024;35(1):1-10. **3.** Villa-Suárez JM, García-Fontana C, Andújar-Vera F, et al. Hypophosphatasia: a unique disorder of bone mineralization. *Int J Mol Sci*. 2021;22(9):4303. **4.** Dahir K,Nunes M. Hypophosphatasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington; 2007. Updated March 27, 2025. Accessed November 5, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1150/ **5.** Vieira LHR, Peixoto KC, Flósi CL, de Farias MLF, Madeira M. Active search of adult patients with persistently low serum alkaline phosphatase levels for the diagnosis of hypophosphatasia. *Arch Endocrinol Metab*. 2021;65(3):289-294. **6.** Seefried L, Genest F, Hofmann C, Brandi ML, Rush E. Diagnosis andtreatment of hypophosphatasia. *Calcif Tissue Int*. 2025;116(1):46. **7.** Levitt MD, Hapak SM, Levitt DG. Alkaline phosphatase pathophysiology with emphasis on the seldom-discussed role of defective elimination in unexplained elevations of serum ALP – a case report and literature review. *Clin Exp Gastroenterol*. 2022;15:41-49. **8.** Schini M, Nicklin P, Eastell R. Establishing race-, gender- and age-specific reference intervals for pyridoxal 5′-phosphate in the NHANES population to better identify adult hypophosphatasia. *Bone*. 2020;141:115577. **9.** Rockman-Greenberg C. Hypophosphatasia. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **10.** Whyte MP. Hypophosphatasia: nature's window on alkaline phosphatase function in humans. In: Bilezikian JP, Raisz LG, Martin TJ, eds. *Principles of Bone Biology*. 3rd ed. Academic Press; 2008:1573-1598. **11.** Aetna. Medical clinical policy bulletin. Asfotase alfa (STRENSIQ). February 12, 2016. Updated December 12, 2024. Accessed November 5, 2025. https://www.aetna.com/cpb/medical/data/900_999/0901.html **12.** Dahir KM, Kishnani PS, Martos-Moreno GÁ, et al. Impact of muscular symptoms and/or pain on disease characteristics, disability, and quality of life in adult patients with hypophosphatasia: a cross-sectional analysis from the Global HPP Registry. *Front Endocrinol (Lausanne)*. 2023;14:1138599. **13.** Dahir KM, Dunbar NS. Medical management of hypophosphatasia: review of data on asfotase alfa. *Curr Osteoporos Rep*. 2025;23(1):14.

STRENSIQ® (asfotase alfa) SELECT IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS

- **Life-threatening hypersensitivity reactions, including anaphylaxis**, have been reported in STRENSIQ-treated patients. Signs and symptoms consistent with anaphylaxis included difficulty breathing, choking sensation, nausea, periorbital edema, and dizziness. These reactions have occurred within minutes after subcutaneous administration of STRENSIQ and have been observed more than 1 year after treatment initiation. Other hypersensitivity reactions have also been reported in STRENSIQ-treated patients, including vomiting, fever, headache, flushing, irritability, chills, erythema, rash, pruritus, and oral hypoesthesia. Consider the risks and benefits of re-administering STRENSIQ following a severe reaction. If the decision is made to re-administer, monitor patients for a reoccurrence of signs and symptoms of a severe hypersensitivity reaction.
- **Lipodystrophy:** Localized lipodystrophy, including lipoatrophy and lipohypertrophy has been reported at injection sites after several months in patients treated with STRENSIQ in clinical trials. Advise patients to follow proper injection technique and to rotate injection sites.
- **Ectopic Calcifications:** Patients with HPP are at increased risk for developing ectopic calcifications. Events of ectopic calcification, including ophthalmic (conjunctival and corneal) and renal (nephrocalcinosis, nephrolithiasis), have been reported in the clinical trial experience with STRENSIQ. There was insufficient information to determine whether the reported events were consistent with the disease or due to STRENSIQ. No visual changes or changes in renal function were reported resulting from the occurrence of ectopic calcifications.

  Ophthalmology examinations and renal ultrasounds are recommended at baseline and periodically during treatment with STRENSIQ to monitor for signs and symptoms of ophthalmic and renal ectopic calcifications and for changes in vision or renal function.
- **Possible Immune-Mediated Clinical Effects:** In clinical trials, most STRENSIQ-treated patients developed anti-asfotase alfa antibodies and neutralizing antibodies which resulted in reduced systemic exposure of asfotase alfa. In postmarketing reports, some STRENSIQ-treated patients with initial therapeutic response subsequently developed recurrence and worsening in disease-associated laboratory and radiographic biomarkers (some in association with neutralizing antibodies) suggesting possible immune-mediated effects on STRENSIQ's pharmacologic action resulting in disease progression. The effect of anti-asfotase alfa antibody formation on the long-term efficacy of STRENSIQ is unknown. There are no marketed anti-asfotase alfa antibody tests. If patients experience progression of HPP symptoms or worsening of disease-associated laboratory and imaging biomarkers after a period of initial therapeutic response to STRENSIQ, consider obtaining anti-asfotase alfa antibody testing by contacting STRENSIQ Medical Information at Alexion at 1-888-765-4747 or by email at medinfo@alexion.com. Close clinical follow up is recommended.

ADVERSE REACTIONS

In clinical trials, the most common adverse reactions (≥ 10%) reported were injection site reactions (63%), lipodystrophy (28%), ectopic calcifications (14%), and hypersensitivity reactions (12%). Possible immune-mediated clinical effects have been identified during post-approval use of STRENSIQ.

DRUG INTERACTIONS

Drug Interference with Laboratory Tests:

- Laboratory tests utilizing alkaline phosphatase (ALP) as a detection reagent could result in erroneous test results for patients receiving treatment due to the presence of asfotase alfa in clinical laboratory samples. Inform laboratory personnel that the patient is being treated with STRENSIQ and discuss use of an alternative testing platform which does not utilize an ALP-conjugated test system.
- Elevated serum ALP measurements detected through clinical laboratory testing are expected in patients receiving STRENSIQ due to circulating concentrations of asfotase alfa. Do not rely on serum ALP measurements for clinical decision making in patients treated with STRENSIQ.

SPECIAL POPULATIONS

- **Pregnancy & Lactation:** There are no available data on STRENSIQ use in pregnant women, the presence of STRENSIQ in human milk, or the effects on the breastfed infant or on milk production, to inform a drug associated risk.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Please see full Prescribing Information for STRENSIQ (asfotase alfa), including Boxed WARNING regarding hypersensitivity reactions including anaphylaxis.

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