Sample Appeal Letter for STRENSIQ® (asfotase alfa) for perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)[1]

When a payer (health plan or pharmacy benefit manager [PBM]) denies a Prior Authorization (PA), precertification, or reauthorization request for STRENSIQ prescribed for the treatment of perinatal/infantile- and juvenile-onset hypophosphatasia (HPP), your patient has the right to appeal the decision. If your patient wishes to appeal, you and your staff may assist by submitting an appeal letter and supporting documentation.

As part of the appeals process, payers may request additional documentation from you to support coverage of STRENSIQ when approval for its use has been denied. Your letter should explain why STRENSIQ is medically necessary for the specific patient and may include supporting documentation. The letter may be submitted in response to the denial letter or to a payer's request for additional documentation. The letter should include patient-specific information, address the reason for denial, be presented on the prescriber's letterhead, and be signed by the prescriber. The provided Sample Appeal Letter gives you a framework for composing an appeal.

The Sample Appeal Letter is provided for informational purposes only and is not 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.

INDICATION

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

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)]*.

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.

General Tips for Completing an Appeal Letter

Understand the appeals process for the specific payer. It's important to follow the payer's guidelines when submitting an appeal. Payers may have their own appeal request forms, which are usually available on their website. If a form is required, include it with your own letter. Be sure to contact the payer with any questions and to obtain written instructions for their appeals process.

When submitting an appeal, timing is critical. Refer to the denial letter to find the timelines for submitting the appeal, as well as any payer-specific guidelines.

In cases of medical urgency, your patient may request an expedited review and can expect to receive a decision within 72 hours. For more information, please visit HealthCare.gov.

Understand the reason for denial. It's important to read the denial letter carefully to understand the reason(s) provided. You may also call the payer to discuss a denial with them; this may help inform you about ways to resolve it in a timely manner.

- **If the denial is due to inaccurate or incomplete information,** carefully review the PA or reauthorization request that you submitted to identify information that is incorrect or was omitted. Resubmit the PA or reauthorization request when all the required information is accurate and complete
- **If there is a medical reason for the denial,** ensure that your Appeal Letter includes specific and relevant medical information to support STRENSIQ use according to the payer's criteria. Your letter should clearly explain why you believe STRENSIQ is the most appropriate option for this patient

Provide all supporting documentation at the same time and in the requested order, as shown in the individual payer's appeal instructions. This might include:

- The payer's appeal form (if required)
- Your Appeal Letter
- A copy of the payer's denial letter
- Supporting documentation, such as clinical notes, lab results, etc

Our dedicated Field Reimbursement Managers (FRMs) can work with you

In the event of a PA denial, FRMs can provide you or your office staff with educational support and guidance. FRMs can help with:

- Payer options for PA resubmission, including details about the resubmission process, peer-to-peer review, appeals process, and associated timelines
- Review of the redacted denial letter or Explanation of Benefits (EOB) letter to provide specific guidance on next steps and best practices

[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 PBM]
[Address]
[City, State, ZIP Code]

Re: [First/Second]-Level Appeal for Coverage Denial of STRENSIQ® (asfotase alfa)
[Request for Expedited Review Due to Medical Urgency]

Denial Letter Date: [MM/DD/YYYY]
Denial Reference #: [Denial Reference #]

Patient: [Name]
Date of Birth: [MM/DD/YYYY]
Member ID Number: [Insurance ID Number] Group Number: [Insurance Group Number]
Rx Bin: [Rx Bin Number] Rx PCN: [Rx PCN Number] Rx Group: [Rx Group Number]

Dear [Contact Name],

I am writing to appeal the coverage denial for [name of patient]'s treatment with STRENSIQ® (asfotase alfa) for [perinatal/infantile-onset OR juvenile-onset] hypophosphatasia (HPP). In the letter referenced above, you stated that the reason for denial was [insert reason for denial]. This letter provides information about my patient's medical history and my treatment rationale.

1 REASON(S) FOR DENIAL AND EXPLANATION

In the appeal letter, you need to address every denial reason(s) stated in the denial letter from the insurance plan. Clearly explain why the reason(s) stated by the insurance plan as a cause for denial of coverage do not preclude a diagnosis of HPP. Refer to "Common Reasons for Denial and Potential Explanations" and "Resources Available to You" on pages 5-7. During the appeal process, it is generally not helpful to provide additional information beyond the specific denial reasons.

In my medical opinion, STRENSIQ remains the most appropriate treatment for [name of patient]. The stated reason(s) for denial was/were: [insert each denial reason, addressing each reason point by point (refer to "Common Reasons for Denial and Potential Explanations" and "Resources Available to You" on pages 5-7 for some examples). Provide any laboratory results if applicable].

2 SUMMARY AND OPTIONAL MEDICAL HISTORY

After addressing each stated reason for denial, you may wish to summarize your appeal and restate your patient's relevant medical history. You may wish to consult the *Common Prior Authorization Criteria for STRENSIQ* resource for an abbreviated list of common signs and symptoms of HPP.

As stated in my initial authorization request, [name of patient] presented with [insert specific clinical signs and symptoms – eg, bone and joint pain, slow-healing fractures, early tooth loss, etc]. These current symptoms, medical history, and patient's [insert relevant laboratory values – eg, persistently low age- and sex-adjusted ALP levels; conclusive *ALPL* gene mutation, etc] confirm a diagnosis of hypophosphatasia, for which the medically necessary treatment is STRENSIQ.[2,3]

For the above reasons, I request that you reverse the coverage determination.

3 For your additional information, I am enclosing [list enclosures, such as a copy of the denial letter, supporting clinical documentation, etc]. If you have any further questions, please feel free to call me at [physician's telephone number] to discuss.

Thank you in advance for your immediate attention to this request.
[Physician's Name, Degree Initials]
[Provider Identification Number]
[Physician's Practice Name]
[Physician's Phone Number]
[Physician's Fax Number]
[Physician's Email]

ATTACHMENTS
At the bottom of your letter, list the items you have enclosed. Be sure to include every article that you referenced or any new documentation.

Attachments:
[Original denial letter]
[Referenced article]
[STRENSIQ Full Prescribing Information]
[STRENSIQ FDA Approval Letter for perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)]

1 Some Common Reasons for Denial and Potential Explanations

Below are some common reasons your patient's PA, precertification, or reauthorization request may be denied. In your appeal letter, ensure that each reason for denial is addressed by sharing your medical expertise on why the requirement should not apply in your patient's individual case. Be sure to attach the supporting references and any additional documentation in your reply.

Denial due to normal levels of PLP: Refer to the articles in the "PLP (Vitamin B_6): Reference Ranges" section and the "PLP (Vitamin B_6): Variability Between Patients" section of the *Compendium of Hypophosphatasia (HPP) References for STRENSIQ* for additional information that can be found at alexionaccessnavigator.com/strensiq

- PLP testing may be used to support the diagnosis but may not be elevated in every patient with HPP.[2] Two factors can confound the evaluation of PLP levels: (1) PLP levels vary greatly in patients with HPP depending on individual symptoms or the severity of the disease, and (2) the reference ranges for PLP may vary between laboratories[4-8]

Denial due to negative or undetectable genetic test for *ALPL*: Refer to the articles in the "Genetic Testing: Negative Test Result/Undetectable Mutations" section of the *Compendium of Hypophosphatasia (HPP) References for STRENSIQ* for additional information

- Patients with low levels of TNSALP may have no detectable mutations. Some mutations remain undetected because of the type of mutation (eg, deletion) or the location of the mutation (eg, deep intronic or regulatory regions). Therefore, the lack of an identified *ALPL* mutation should not preclude diagnosis or management of HPP[9-12]

Denial due to positive genetic test with heterozygous mutation: Refer to the articles in the "Genetic Testing: Heterozygous Mutation" section of the *Compendium of Hypophosphatasia (HPP) References for STRENSIQ* for additional information

- *Patients with heterozygous mutations can have juvenile-onset HPP*
  - Of the 14 patients enrolled in the phase 3 study with a monoallelic (heterozygous) variant, 13 of 14 had juvenile-onset of symptoms[13]
- *Patients with heterozygous mutations may have a substantial disease burden*
  - Adults and adolescents with HPP experience a substantial burden of illness, regardless of inheritance pattern or variant state (biallelic or monoallelic)[13]
  - *ALPL* variant state (biallelic or monoallelic) generally does not appear to impact the burden of HPP disease as shown in a pooled analysis of two phase 2, randomized, open-label studies in adolescents and adults with HPP[13]
- *Patients with heterozygous mutations should be treated with STRENSIQ*
  - STRENSIQ is the first and only approved therapy for HPP[14]
  - The treatment with asfotase alfa (N=19) for up to 5 years normalized TNSALP substrate levels and improved functional outcomes, with no clear differences between variant states[13]

Denial due to variant of unknown significance: Refer to the articles in the "Genetic Testing: Variant of Unknown Significance" section of the *Compendium of Hypophosphatasia (HPP) References for STRENSIQ* for additional information

- Not all patients with HPP will have a conclusive test with identifying mutations. New mutations are still being discovered, and rare or novel variants may have an unknown significance, limiting the utility of genetic testing as a diagnostic tool[3,10]

Denial due to lack of records of perinatal/infantile- or juvenile-onset HPP: Refer to the articles in the "Clinical Diagnosis & Treatment of HPP" section of the *Compendium of Hypophosphatasia (HPP) References for STRENSIQ* for additional information

- STRENSIQ is indicated for the treatment of perinatal/infantile- and juvenile-onset HPP. As such, evidence of onset during childhood or adolescence must be provided. You may consider attaching medical records of early symptoms such as premature tooth loss, short stature, bowed legs, missed motor milestones, abnormal gait, or failure to thrive[1,2]
- If medical records are not available, patient attestations to their symptoms or photographs may be submitted. Check with your patient's plan or ask an Alexion FRM for examples
- Please note that in some cases, official state guidelines for record-keeping may prevent a patient from obtaining such documentation. If this situation applies to your patient, they or their caregivers can write a letter sharing what the guidelines and limitations are

Denial due to the absence of skeletal manifestations: Refer to the article in the "HPP in the Absence of Skeletal Manifestations" section of the *Compendium of Hypophosphatasia (HPP) References for STRENSIQ* for additional information

- Adult patients with HPP may experience disability, mobility issues, and burden of disease regardless of skeletal involvement[15]
- A clinical diagnosis of HPP can be made in the absence of skeletal manifestations[15]
    - In an analysis of a multinational registry study, ~20% (73 of 373) of adult patients with confirmed HPP presented with only muscular and/or pain signs and symptoms. As patients with HPP may present without skeletal manifestations, it is important to conduct a thorough assessment when diagnosing and/or managing a patient with suspected HPP[15]

Denial due to missing documentation that was not previously required: Insurance plans and PBMs may change their requirements for approving authorization requests, even if a patient has previously been approved in the past. If the documents currently being requested were not required for initial authorization or previous reauthorizations, consider requesting an exception to the new requirement with the understanding that future reauthorizations should conform to the requirements. Insurance plans may also accept other documentation to support clinical improvement with STRENSIQ. Check with your patient's plan or ask an Alexion FRM for examples

2 Optional Medical History

While not necessary, you may find it helpful to include your patient's medical history in the appeal letter. It is recommended to keep the medical history in an appeal letter as succinct as possible, with only the most clinically significant facts repeated, such as[3]:

- Current symptoms: eg, bone and joint pain, muscular symptoms
- Supportive lab results: eg, persistently low age- and sex-adjusted ALP levels; conclusive *ALPL* gene mutation
- Patient history: eg, skeletal abnormalities, family history of HPP

3 Attachments and Supporting Documentation

In the appeal, you only need to include the original appeal letter and new supporting documentation. If you referred to any specific articles or obtained any photographs or attestations, be sure to attach them to the appeal

Resources Available to You

- The *Common Prior Authorization Criteria for STRENSIQ* resource provides you with information about common criteria used by payers to make prior authorization decisions for STRENSIQ for HPP
- The *Compendium of Hypophosphatasia (HPP) References for STRENSIQ* provides information about specific scientific data and publications that may provide additional evidence for your Appeal Letter

When preparing an Appeal Letter, ensure that you have provided specific and relevant medical information to support appropriate use according to the payer's criteria. Include other documentation, as appropriate, such as clinical records, lab reports, and the STRENSIQ full Prescribing Information.

References: 1. STRENSIQ. Package insert. Alexion Pharmaceuticals, Inc. **2.** Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **3.** Mornet E, Nunes ME. Hypophosphatasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington; 2007. Accessed July 7, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1150/ **4.** 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. **5.** Mayo Clinic Laboratories. Test Definition: PLP. Accessed July 7, 2022. https://www.mayocliniclabs.com/test-catalog/download-setup.php?format=pdf&unit_code=42359 **6.** Labcorp. Vitamin B_6, Plasma. Accessed July 7, 2022. https://www.labcorp.com/tests/004655/vitamin-b-sub-6-sub-plasma **7.** CADTH. Asfotase alfa. Updated July 20, 2015. Accessed July 7, 2022. https://www.cadth.ca/asfotase-alfa **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.** Hypophosphatasia. Orphanet. Updated February 2020. Accessed July 7, 2022. https://www. orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_ id=162&Disease(s)/group%20of%20diseases=Hypophosphatasia&title=Hypophosphatasia&search=Disease_Search_Simple **10.** Riancho-Zarrabeitia L, García-Unzueta M, Tenorio JA, et al. Clinical, biochemical and genetic spectrum of low alkaline phosphatase levels in adults. *Eur J Intern Med*. 2016;29:40-45. **11.** Mornet E. Hypophosphatasia. *Metabolism*. 2018;82:142-155. **12.** Taillandier A, Domingues C, De Cazanove C, et al. Molecular diagnosis of hypophosphatasia and differential diagnosis by targeted Next Generation Sequencing. *Mol Genet Metab*. 2015;116(3):215-220. **13.** Kishnani PS, Del Angel G, Zhou S, Rush ET. Investigation of ALPL variant states and clinical outcomes: an analysis of adults and adolescents with hypophosphatasia treated with asfotase alfa. *Mol Genet Metab*. 2021;133(1):113-121. **14.** STRENSIQ BLA 125513/0. US Food and Drug Administration, Department of Health and Human Services. Updated October 23, 2015. Accessed October 3, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125513Orig1s000ltr.pdf **15.** Dahir KM, Kishnani PS, Martos-Moreno GA, 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.

IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

ALEXION®
AstraZeneca Rare Disease

US/STQ-H/0212 V4 05/2024

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