A Compendium of Hypophosphatasia (HPP) References for STRENSIQ® (asfotase alfa)

When completing a letter of medical necessity or appeal request for STRENSIQ indicated for the treatment of perinatal/infantile- and juvenile-onset HPP, insurers may require documentation, including clinical notes and impressions, lab results, and other relevant information. The selection of references below, including the STRENSIQ Prescribing Information and published literature, may be helpful when completing the request to your patient's insurance company.

Some of the literature listed below may include content that is not included in the FDA-approved US Full Prescribing Information for STRENSIQ. Please refer to the Indication and Important Safety Information for STRENSIQ on pages 1, 3, and 4 and the accompanying **US Full Prescribing Information** when completing the request.

This compendium is not inclusive of all US and global data and literature for STRENSIQ for the treatment of perinatal/infantile- and juvenile-onset HPP. Alexion does not warrant, promise, guarantee, or make any statement that the use or citation of any literature listed below will result in coverage or payment for STRENSIQ.

Abstracts for the references cited below are available online. Most of the publications permit access and download of the articles for personal use; some publications require that the article be purchased in order to gain access.

For ease of use, each reference is categorized by topic, as follows:

Clinical Diagnosis, Management, and Treatment Monitoring of HPP

Bianchi ML. Hypophosphatasia: an overview of the disease and its treatment. *Osteoporos Int*. 2015;26(12):2743-2757.

Bianchi ML, Bishop NJ, Guañabens N, et al. Hypophosphatasia in adolescents and adults: overview of diagnosis and treatment. *Osteoporos Int*. 2020;31(8):1445-1460.

Bishop N, Munns CF, Ozono K. Transformative therapy in hypophosphatasia. *Arch Dis Child*. 2016;101(6):514-515.

Colazo JM, Hu JR, Dahir KM, Simmons JH. Neurological symptoms in hypophosphatasia. *Osteoporos Int*. 2019;30(2):469-480.

Högler W, Langman C, Gomes da Silva H, et al. Diagnostic delay is common among patients with hypophosphatasia: initial findings from a longitudinal, prospective, global registry. *BMC Musculoskelet Disord*. 2019;20(1):80.

Khan A, Josse R, Kannu P, et al. Hypophosphatasia: Canadian update on diagnosis and management. *Osteoporos Int*. 2019;30:1713-1722.

Kishnani P, Rush E, Arundel P, et al. Monitoring guidance for patients with hypophosphatasia treated with asfotase alpha. *Mol Genet Metab*. 2017;122(1-2):4-17.

Michigami T, Ohata Y, Fujiwara M, et al. Clinical practice guidelines for hypophosphatasia. *Clin Pediatr Endocrinol*. 2020;29(1):9-24.

Rockman-Greenberg C. Hypophosphatasia. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388.

INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **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, skin erythema, rash, pruritus and oral hypoesthesia.

Please see additional Important Safety Information on page 3 and page 4 and full Prescribing Information for STRENSIQ (asfotase alfa).

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

Genetic Testing and Diagnostic Criteria

McKiernan FE, Dong J, Berg RL, et al. Mutational and biochemical findings in adults with persistent hypophosphatasemia. *Osteoporos Int*. 2017;28(8):2343-2348.

Mornet E, Nunes ME. Hypophosphatasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington; 2007. Accessed July 6, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1150/

Mornet E, Taillandier A, Domingues C, et al. Hypophosphatasia: a genetic-based nosology and new insights in genotype-phenotype correlation. *Eur J Hum Genet*. 2021;29(2):289-299.

Genetic Testing: Negative Test Result/Undetectable Mutations

Hypophosphatasia. Orphanet. Updated February 2020. Accessed July 6, 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

Mornet E. Hypophosphatasia. *Metabolism*. 2018;82:142-155.

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.

Genetic Testing: Variant of Unknown Significance

Mornet E, Nunes ME. Hypophosphatasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington; 2007. Accessed July 6, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1150/

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.

Genetic Testing: Heterozygous Mutation

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.

PLP (Vitamin B_6): Reference Ranges

Canadian Agency for Drugs and Technologies in Health. Asfotase alfa (Strensiq). In: *Common Drug Review*. Canadian Agency for Drugs and Technologies in Health; 2017. Accessed July 6, 2022. https://www.ncbi.nlm.nih.gov/books/NBK476046/

Incyte Diagnostics. Pyridoxal 5-Phosphate (PLP), Plasma. Accessed August 3, 2022. https://www.incytediagnostics.com/laboratory-services/test-directory/TestDetails/pyridoxal-5-phosphate-plp-plasma

Laboratory Medicine & Medicine Pathology. Vitamin B_6. Accessed August 3, 2022. https://testguide.labmed.uw.edu/public/view/RVITB6

Labcorp. Vitamin B_6, plasma. Accessed July 6, 2022. https://www.labcorp.com/tests/004655/vitamin-b-sub-6-sub-plasma

Mayo Clinic Laboratories. Pyridoxal 5-phosphate (PLP), plasma. Accessed July 6, 2022. https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/42359

Schini M, Nicklin P, and 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.

PLP = pyridoxal 5'-phosphate.

Please see additional Important Safety Information on page 1, page 3, and page 4 and full Prescribing Information for STRENSIQ (asfotase alfa).

PLP (Vitamin B_6): Variability Among Patients

Schmidt T, Mussawy H, Rolvien T, et al. Clinical, radiographic and biochemical characteristics of adult hypophosphatasia. *Osteoporos Int*. 2017;28(9):2653-2662.

Whyte MP. Hypophosphatasia: nature's window on alkaline phosphatase function in humans. In: Bilezikian J, Raisz L, Martin JT, eds. *Principles of Bone Biology*. 3rd ed. Academic Press; 2008:1573-1598.

PEA: Variability Among Patients

Mayo Clinic Laboratories. Amino acids, quantitative, random, urine. Accessed July 6, 2022. https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/60475

Phosphoethanolamine; urine. Doctor's Data, Inc. Accessed July 6, 2022. https://www.doctorsdata.com/analyte/Phosphoethanolamine/Urine%20Amino/Phosphoethanolamine%3B%20urine

Whyte MP. Hypophosphatasia: nature's window on alkaline phosphatase function in humans. In: Bilezikian J, Raisz L, Martin JT, eds. *Principles of Bone Biology*. 3rd ed. Academic Press; 2008:1573-1598.

STRENSIQ Prescribing Information and Published Pivotal Studies in HPP

Hofmann CE, Harmatz P, Vockley J, et al. Efficacy and safety of asfotase alfa in infants and young children with hypophosphatasia: a phase 2 open-label study. *J Clin Endocrinol Metab*. 2019;104(7):2735-2747.

Kishnani PS, Rockman-Greenberg C, Rauch F, et al. Five-year efficacy and safety of asfotase alfa therapy for adults and adolescents with hypophosphatasia. *Bone*. 2019;121:149-162.

STRENSIQ. Prescribing Information. Alexion Pharmaceuticals, Inc. **https://alexion.com/documents/strensiq_uspi.pdf**

STRENSIQ BLA 125513/0. US Food and Drug Administration, Department of Health and Human Services. October 23, 2015. Accessed July 6, 2022. https://www.https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125513Orig1s000ltr.pdf

Whyte MP, Simmons JH, Moseley S, et al. Asfotase alfa for infants and young children with hypophosphatasia: 7 year outcomes of a single-arm, open-label, phase 2 extension trial. *Lancet Diabetes Endocrinol*. 2019;7(2):93-105.

Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med*. 2012;366(10):904-913.

Whyte MP, Rockman-Greenberg C, Ozono K, et al. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. *J Clin Endocrinol Metab*. 2016;101(1):334-342.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Inform patients and/or caregivers of the signs and symptoms of hypersensitivity reactions and have them seek immediate medical care should signs and symptoms occur. If a severe hypersensitivity reaction occurs, discontinue STRENSIQ treatment and initiate appropriate medical treatment. Consider the risks and benefits of re-administering STRENSIQ to individual patients following a severe reaction. If the decision is made to re-administer the product, monitor patients for a reoccurrence of signs and symptoms of a severe hypersensitivity reaction.

- **Lipodystrophy:** Localized lipodystrophy, including lipoatrophy (depression in the skin) and lipohypertrophy (enlargement or thickening of tissue), 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.

PEA = phosphoethanolamine; PLP = pyridoxal 5'-phosphate

Please see additional Important Safety Information on page 1 and page 4 and full Prescribing Information for STRENSIQ (asfotase alfa).

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

- **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 or not 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

Overall, the most common adverse reactions (≥ 10%) reported were injection site reactions (63%). Other common adverse reactions included 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 and may be unreliable for clinical decision making.

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.

Please see Indication & additional Important Safety Information on page 1 and page 3 and full Prescribing Information for STRENSIQ (asfotase alfa).

ALEXION®
AstraZeneca Rare Disease

10/2022 US/STQ-H/0340

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