



Hypophosphatasia Signs and Symptoms Checklist

This simplified guide is intended to aid in documenting observed/reported history of signs and symptoms for patients who are diagnosed with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP). HPP is an inherited, multisystemic, rare metabolic disorder characterized by deficient alkaline phosphatase activity that may progress over time.¹⁻⁴

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 hyposthesia. 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.

Please see additional Important Safety Information throughout and full [Prescribing Information](#) for STRENSIQ (asfotase alfa), including Boxed WARNING regarding hypersensitivity reactions including anaphylaxis.

Hypophosphatasia Signs and Symptoms Checklist

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 product label. Attaching the checklist is not sufficient documentation of HPP for many payers.

Signs/Symptoms

(This list may not be exhaustive and all patients may not present the same way.⁵ Treatment may not have an impact on all the signs and symptoms listed and inclusion below does not imply efficacy.)

		Currently presenting with	History of symptoms prior to age 18
 Neurologic	Vitamin B ₆ -responsive seizures (in infants) ¹	☐	☐
	Increased intracranial pressure (in infants) ^{1,6-9}	☐	☐
	Headaches ^{4,8,9}	☐	☐
	Mood (anxiety, depression) ^{4,8,9}	☐	☐
 Dental	Premature tooth loss/nontraumatic tooth loss (with root intact) ^{1,4}	☐	☐
	Poor/abnormal dentition ^{1,4}	☐	☐
 Skeletal/Orthopedic	Hypomineralization ⁷	☐	☐
	Skeletal deformities (eg, enlarged wrist and ankle joints, abnormal skull shape) ¹	☐	☐
	Fractures/pseudofractures (slow to heal) ^{1,4,10-12}	☐	☐
	Craniosynostosis (in infants) ^{1,6,7}	☐	☐
	Rachitic chest (in infants) ^{1,6,13}	☐	☐
	Rickets ¹	☐	☐
	Bowed legs or knock knees ¹	☐	☐
	Bone pain ¹	☐	☐
	Osteomalacia ^{1,7}	☐	☐

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

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Signs/Symptoms

(This list may not be exhaustive and all patients may not present the same way.⁵ Treatment may not have an impact on all the signs and symptoms listed and inclusion below does not imply efficacy.)

		Currently presenting with	History of symptoms prior to age 18
 Growth/ Development (children)	Failure to thrive ^{1,4}	☐	☐
	Delayed/missed motor milestones ^{1,4}	☐	☐
	Short stature ¹	☐	☐
 Respiratory (in infants)	Respiratory failure ^{1,4,7,14}	☐	☐
	Respiratory complications (eg, respiratory support) ¹⁵	☐	☐
	Respiratory problems (eg, pneumonia) ¹⁴	☐	☐
 Muscular/ Rheumatologic	Muscle weakness ¹	☐	☐
	Fatigue ⁸	☐	☐
	Hypotonia ¹	☐	☐
	Muscle/joint pain ¹	☐	☐
	Delayed walking ^{1,10}	☐	☐
	Waddling gait ^{1,10}	☐	☐
	Pseudogout ^{4,15}	☐	☐
 Renal	Hypercalcemia ^{4,15-17}	☐	☐
	Hypercalciuria ^{4,15-17}	☐	☐
	Nephrocalcinosis ^{4,15-17}	☐	☐

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- 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.

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The Alexion support service team is here to help you and your patients navigate this journey.



Your Alexion Field Reimbursement Manager (FRM) is available to help assist you in this process and answer any questions you may have about your patient's insurance policy requirements.

Name: []
Phone: []
Email: []



Alexion Access Navigator is a dedicated resource website for US HCPs and their offices that contains downloadable access and reimbursement materials for STRENSIQ.

www.AlexionAccessNavigator.com/Strensiq

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

In clinical trials, the most common adverse reactions ($\geq 10\%$) 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

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References: 1. Rockman-Greenberg C. *Pediatr Endocrinol Rev.* 2013;10(suppl 2):380-388. 2. McKiernan FE, et al. *J Bone Miner Res.* 2014;29(7):1651-1660. 3. Rush ET, et al. *Orphanet J Rare Dis.* 2019;14(1):201. 4. Kishnani PS, et al. *Mol Genet Metab.* 2017;122(1-2):4-17. 5. Mornet E. *Metabolism.* 2018;82:142-155. 6. Whyte MP. *Nat Rev Endocrinol.* 2016;12(4):233-246. 7. Bishop N, et al. *Arch Dis Child.* 2016;101(6):514-515. 8. Bianchi ML, et al. *Osteoporos Int.* 2020;31(8):1445-1460. 9. Colazo JM, et al. *Osteoporos Int.* 2019;30(2):469-480. 10. Whyte MP. Hypophosphatasia: nature's window on alkaline phosphatase function in humans. In: Bilezikian J, Raisz L, Martin TJ, eds. *Principles of Bone Biology.* 3rd ed. Academic Press; 2008:1573-1598. 11. NORD. Hypophosphatasia. Accessed March 30, 2023. <https://rarediseases.org/rare-diseases/hypophosphatasia/> 12. Mornet E, Nunes ME. Hypophosphatasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*®. University of Washington; 2007. Accessed March 30, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK1150/> 13. Whyte M. In: Thakker RV, et al, eds. *Genetics of Bone Biology and Skeletal Disease.* Academic Press; 2013:337-360. 14. Whyte MP, et al. *J Pediatr.* 2019;209:116-124.e4. 15. Höglér W, et al. *BMC Musculoskelet Disord.* 2019;20(1):80. 16. Weber TJ, et al. *Metabolism.* 2016;65(10):1522-1530. 17. Fallon MD, et al. *Medicine (Baltimore).* 1984;63(1):12-24.



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US/STQ-H/0498 V2 07/2024