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

Identifying and Diagnosing Hypophosphatasia (HPP)

A patient discussion guide and diagnostic testing resource

HPP is an inherited, multisystemic, rare metabolic disorder characterized by deficient alkaline phosphatase (ALP) activity that may progress over time and potentially become debilitating.[1-6]

This booklet contains both a **discussion guide** for you and your patients to help identify the burden of HPP and uncover current or past signs and symptoms, and a **reference resource for the routine tests** you can use to help support a diagnosis of perinatal/infantile- and juvenile-onset HPP in your patients.

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.

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

What to look for: Possible signs & symptoms

Dental[1,7]

History of premature tooth loss or poor dentition

- Were you missing teeth in any of your preschool photos?
- Beyond regular checkups and cleanings, did you have to go to the dentist a lot for any issues with your teeth or gums?
- Did you have a lot of cavities, or have teeth fall out with the root still intact?

Growth/Development[1,7]

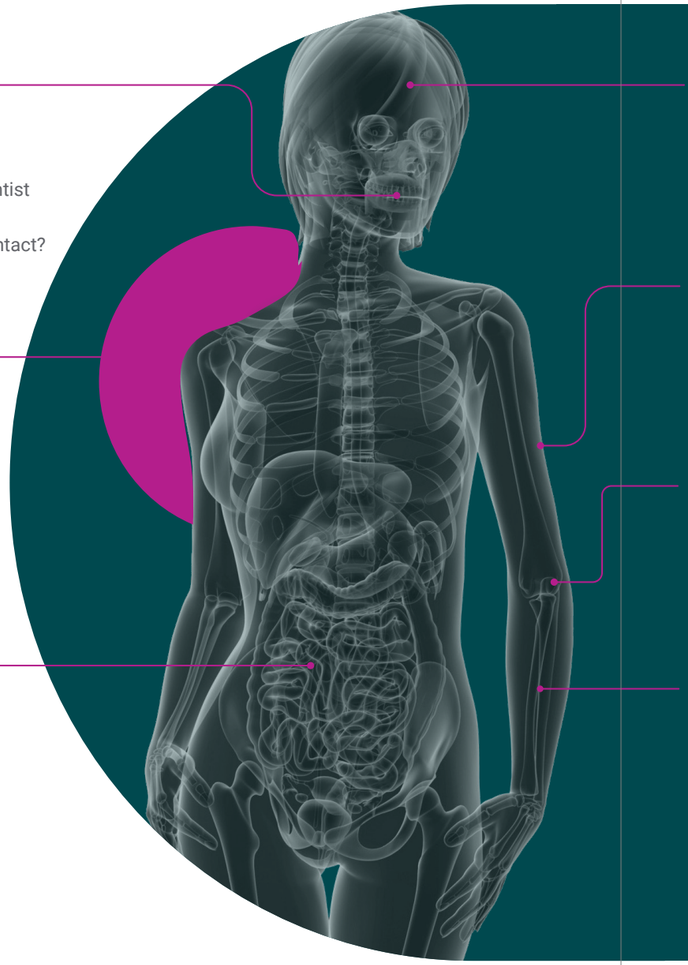
History of failure to thrive and missed motor milestones

- In class pictures, did you appear smaller than most of your classmates?
- Growing up, did you ever hear that you started walking later than your peers?
- Did you ever have trouble keeping up with your peers when playing with them in gym class or other sports?

Renal[2,4]

History of hypercalcemia, hypercalciuria, or nephrocalcinosis

- Have you ever had kidney stones?
- When going to the bathroom, have you ever had urine that was red?



Neurologic[7-9]

History of seizures (in infancy), headaches, mood (anxiety, depression)

- Has your family ever mentioned if you had seizures when you were a baby?
- Do you get headaches frequently, or without any warning?
- Do you have any trouble concentrating, or any feelings of being down or easily irritated?

Muscular[1,7]

Muscle pain or weakness, fatigue, difficulty walking, or waddling gait

- Have your muscles ever been sore or ached for no reason?
- Do you find yourself feeling fatigued or having trouble keeping up with your peers in normal daily activities?
- Do you sway when you walk, or have trouble walking in a straight line?

Rheumatic[2,7]

Pain or pseudogout

- Do you have pain, tenderness, and/or swelling in your joints?
- When you get up in the morning or after sitting around for a while, does it feel like your joints or muscles are stiff?
- When reaching for items around the house, does it ever hurt to reach up or feel like you can't reach all the way?

Skeletal/Orthopedic[1,7,10-12]

Slow to heal fractures, history of rickets (weak/soft bones), bone pain, craniosynostosis, or osteomalacia

- Growing up, did it seem like you broke bones more often, or more easily, than your classmates?
- Have you ever had a fracture or a bone injury that you haven't been able to explain (eg, foot fracture)?
- Do you have bone pain, or pain that gets worse when you move?
- Were you diagnosed with rickets as a child and/or have bowed legs?
- When you were a baby, did you have any skull surgeries or have to wear a helmet?

These questions are for illustrative purposes only and are not representative of all signs or symptoms that may present in patients with HPP.

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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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.

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

What to look for: HPP testing at a glance

HPP can be diagnosed based on persistently low ALP levels and clinical signs and symptoms[7,13]

Persistently low alkaline phosphatase (ALP) activity can be defined as 2 or more age- and sex-adjusted ALP levels below normal range in intervals of more than 30 days. Patients should be evaluated for other symptoms of HPP and differential diagnoses should be ruled out. Persistently low ALP may differentiate HPP from other conditions.[5,9,14]

WHAT IS LOW ALP?

IN ADULTS

<40 U/L

is considered low[15-19]*

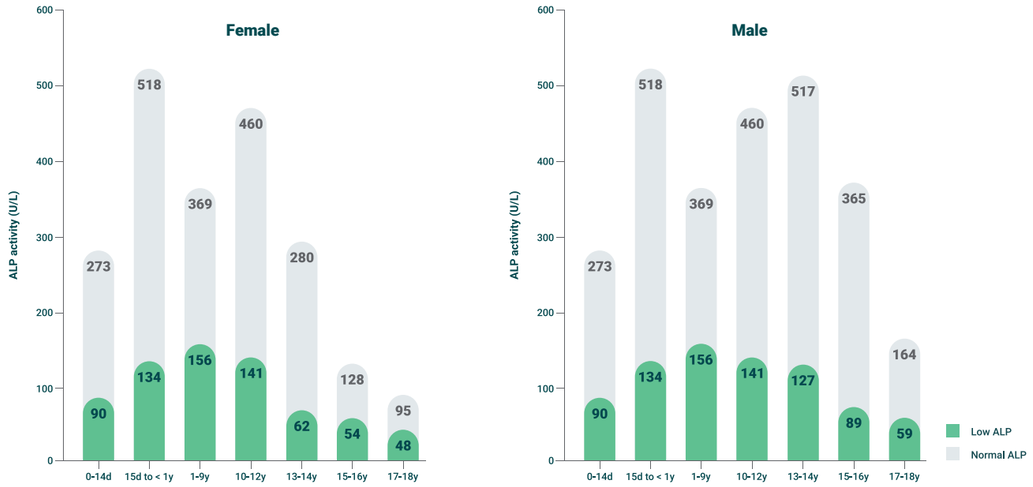
IN CHILDREN

LOW RANGES VARY

based on age and sex[7,13,20]

*Limitations: An alkaline phosphatase level of below 40 U/L is not conclusive for a diagnosis of hypophosphatasia. Patient should be evaluated for other symptoms of hypophosphatasia and differential diagnoses should be ruled out.

Age- and sex-adjusted ALP reference ranges for children (U/L)[20]



Graph adapted from the Canadian Laboratory initiative on Pediatric Reference Intervals (CALIPER) project. CALIPER samples from 1072 male and 1116 female participants (newborn to 18 years) were used to calculate age- and sex-specific reference intervals. No variation in ALP based on ethnic differences was observed. Check with your lab for their appropriate age- and sex-adjusted reference range.

- Clinicians should ensure that reported laboratory results for ALP reflect age- and sex-adjusted reference ranges for the specific patient
- Check with your lab for their appropriate age- and sex-adjusted reference range

Patients with HPP may present with[1,9]:	**Persistently low ↓**	**Elevated ↑**		
	ALP	**PPi†**	**PLP‡**	**PEA§**

- Elevated ALP substrates (PLP or PEA) may help support the diagnosis of HPP, but may not always be elevated in patients with HPP

†PPi (inorganic pyrophosphate) tests are done in research settings only and are not commercially available.[9]

‡PLP (pyridoxal 5'-phosphate) levels may be elevated in individuals taking supplements containing vitamin B_6. PLP levels may also appear as normal, or low in patients with HPP. This does not invalidate the HPP diagnosis.[5,21]

§PEA (phosphoethanolamine) levels may be normal in some patients with HPP. PEA results may be elevated in other bone diseases.[10,22]

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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PLP/vitamin B_6 testing

PLP is the active form of vitamin B_6. In HPP, low ALP activity leads to an accumulation of PLP.[1]

Prepping for testing:

Advise patients to fast overnight. Patients should not take vitamins or dietary supplements for at least 1 week prior to blood draw, as these may affect test results. Note: PLP is bound to albumin and may be affected by nutrition, smoking, inflammation, and drugs[11,21,23-27]

Remember: the test sample must be protected from light in an amber-colored tube, as exposure to light can reduce PLP activity, and maintained at refrigerated or frozen temperature. Timing of collection, storage requirements, and specimen stability information may vary by laboratory.[18,19,21,27-29]

Does your patient have elevated PLP?

Example normal PLP reference ranges[23,II]:

- **Males:** 5.3-46.7 µg/L
- **Females:** 2.0-32.8 µg/L

Elevated PLP levels suggest that your patient may have HPP[15]

Low or normal PLP does not rule out HPP[15]

Urine PEA testing

PEA is a biomarker that may confirm an HPP diagnosis. In patients with HPP, low ALP activity leads to an accumulation of PEA.[1]

Prepping for testing:

Sample collected via spot urine test or 24-hour urine collection test. Note: improper collection or storage of 24-hour urine collection may produce unreliable results such as[9-11,30,31]:

- Incomplete collection (omission of one or more samples in 24 hours)
- Incorrect collection time
- Incomplete emptying of bladder
- Poor storage of sample
- Inclusion of first 2 morning samples

Consult with your lab to discuss how to best collect a PEA sample. Sample type and the timing of collection may differ across labs

Remember that PEA levels can vary through a 24-hour period and are dependent on your patient's age and diet. Samples may be refrigerated or frozen and can be shipped on dry ice[27,32,33]

Ordering PEA:

- PEA analysis is available through select laboratories either as a stand-alone assay or as a special request within an amino acid panel[32-36]
- As part of an amino acid panel, the provider requests PEA analysis either by calling the laboratory or adding a comment on the submission form
- Turnaround time is typically within 1 week, but determined independently per lab[34]

Does your patient have elevated PEA?

Example Normal PEA reference ranges[35,II]:

- **≤12 months:** 15-341 nmol/mg
- **13-35 months:** 33-342 nmol/mg
- **3-6 years:** 19-164 nmol/mg
- **7-8 years:** 12-118 nmol/mg
- **9-17 years:** <88 nmol/mg
- **≥18 years:** <48 nmol/mg

PEA results may be elevated in other metabolic bone diseases, but in the context of low ALP activity and clinical symptoms, elevated PEA may support a diagnosis of HPP. PEA levels may be normal in some patients with HPP.[10,23]

Keep in mind: Reference ranges for PLP and PEA may vary depending on your testing lab. Refer to your lab's specific reference ranges when evaluating test results

IIThis is one example of PLP and PEA reference ranges based on one lab.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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

The role of genetic testing: what you should know

Possible test results

Positive[36-39]	A variant is reported as pathogenic or likely pathogenic, and the result may be consistent with an HPP diagnosis.
Inconclusive[36,39-41]	A variant was found, but its significance to the disease is uncertain (variant of unknown significance or VUS). Inconclusive results *do not* rule out HPP. The variant's classification may change with additional research or publications in the future.
Negative[22,40-43]	The test did not identify a variant or a variant of likely relevance to the disease; this *does not* rule out HPP, and additional genetic testing may be conducted if desired.

What if a test comes back negative?[22,41-45]

If a genetic test comes back negative, remember that identifying a variant is not necessary to diagnose a patient with HPP. Negative test results do not rule out an HPP diagnosis because:

- Some variants may not be detected by the method that was employed (eg, the variant is a large deletion or insertion)
- Some variants may be in a noncoding region, which is typically not sequenced
- New variants are discovered as more patients are tested and diagnosed (more than 400 variants currently discovered)

What can you do?[22]

If initial testing comes back negative, consider performing gene-targeted deletion/duplication analysis to evaluate for exon or whole gene deletions or duplications. Also, consider contacting a geneticist or genetic counselor.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS (cont'd)

Drug Interference with Laboratory Tests: (cont'd)

- 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.

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HPP is an inherited disorder characterized by mutations in the *ALPL* gene.[1]
While a positive *ALPL* genetic test may help to confirm if your patient has HPP, it is NOT required for diagnosis, and a negative result does not rule out HPP.[42]
Genetic testing is not a requirement for STRENSIQ approval by all insurance policies. Please work with your Alexion team to determine if a genetic test is required prior to submitting any paperwork to the specialty pharmacy.

Limitations and challenges[10,11,22,42]

While genetic testing for hypophosphatasia can be a useful tool, it remains an evolving science with certain limitations and challenges:

- Restrictive costs/affordability
- Diagnostic services only available at certain laboratories
- Not all *ALPL* variants necessarily lead to the manifestation of hypophosphatasia or establish hypophosphatasia
- Diagnostic sensitivity of genetic tests that detect *ALPL* can vary by laboratory
- *ALPL* sequencing is predicted to detect pathogenic variants of ~95% of severe perinatal and infantile hypophosphatasia cases; in milder forms, the detection rate is difficult to estimate
- The milder the disease, the higher the likelihood that only one *ALPL* pathogenic variant is detected

Talking to patients about their results

A positive test could be used to confirm HPP. If your patient tests positive for an *ALPL* mutation, encourage them to seek genetic counseling to better understand if others in their family may be affected as well.

Patients with HPP may have a negative *ALPL* test due to various factors. Share other lab results with your patients and talk to them about their symptoms and how a diagnosis of HPP is made.

Looking to learn more?

Most labs offer genetic counseling and testing services. Inquire with your lab regarding complementary genetic counseling availability. Generally, the turnaround time is up to 6 weeks.

Insurance requirements and/or coverage for genetic testing vary by state and insurance provider. Your Alexion Field Reimbursement Manager can help you verify with the patient's insurer to understand which type of services will be covered and what is necessary for STRENSIQ approval.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

Persistently low ALP in the presence of clinical symptoms could mean your patient has HPP[9,13]

Ask your Alexion representative or visit STRENSIQ-hcp.com for information.

Only STRENSIQ gets straight to the source of HPP

Visit STRENSIQ-hcp.com to discover how STRENSIQ may help.

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