PDL DRUG REVIEW

Proprietary Name: Strensiq®
Common Name: asfotase alfa solution
PDL Category: Endocrine Metabolic Agents

Summary

Pharmacology/Usage: Asfotase alfa is a soluble glycoprotein composed of 2 identical polypeptide chains. Strensiq®, a formulation of asfotase alfa, is a tissue non-specific alkaline phosphatase (TNSALP) made by recombinant DNA technology in a Chinese hamster ovary cell line. Hypophosphatasia (HPP) is caused by a deficiency in TNSALP enzyme activity, leading to an increase in several TNSALP substrates including inorganic pyrophosphate (PPi). Elevated levels of PPi block hydroxyapatite crystal growth which inhibits bone mineralization and causes an accumulation of un-mineralized bone matrix. This expresses as rickets and bone deformation in infants/children and as osteomalacia once growth plates close. Replacing TNSALP enzyme with Strensiq® treatment reduces the enzyme substrate levels.

Indication: For the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

While there was no pregnancy category provided, the risk summary indicates there are no available human data on Strensiq® use in pregnant women to inform a drug associated risk. The safety and efficacy of Strensiq® have been established in the pediatric population. The majority of pediatric patients in the clinical trials were aged 1 day to 16 years of age.

Dosage Forms: Injection: 18mg/0.45ml, 28mg/0.7ml, 40mg/ml, or 80mg/0.8ml solution in single-use vials

Recommended Dosage: *Perinatal/Infantile-Onset HPP:* Given as 6mg/kg SQ as either: 2mg/kg TIW OR 1mg/kg 6 times per week. Injection site reactions may limit the tolerability of the 6 times per week regimen. The dose may be increased to a maximum of 9mg/kg per week administered as 3mg/kg SQ 3 times per week. *Juvenile-Onset HPP:* Given as 6mg/kg per SQ as either: 2mg/kg TIW OR 1mg/kg 6 times per week.

Do not use the 80mg/0.8ml vial in pediatric patients weighing <40kg. The SQ dose should be administered within 1 hour upon removal from refrigeration. It is recommended to rotate the site of injection into the abdominal area, thigh, or deltoid. It should not be administered in areas that are reddened, inflamed, or swollen.

Drug Interactions: There are no documented drug interactions.

Common Adverse Drug Reactions: *There was no placebo data available to compare with Strensiq®. The listed % incidence for adverse drug reactions= reported % incidence for Strensiq® in perinatal/infantile-onset HPP clinical trials of a dose ≤6mg/kg per week.* The most frequently reported adverse events included erythema (44%), discoloration/hypopigmentation (17%), pain/tenderness (15%), pruritus/itching (15%), swelling (12%), induration (14%), macule (6%), reaction, not otherwise specified (9%), bruising (9%), nodule (3%), other injection site reactions (15%), injection site atrophy (6%), injection site hypertrophy (8%), other lipodystrophy (6%), vomiting/emesis (3%), and other hypersensitivity reactions (9%). Adverse events reported at rates <1% included hypocalcemia, renal stones, chronic hepatitis, and decreased vitamin B6.

During clinical trials with Strensiq®, 14% reported ectopic calcification of the eye (including the cornea and conjunctiva), and the kidneys (nephrocalcinosis). There was insufficient information to determine if the events were consistent with the disease or due to Strensiq® treatment. It is recommended to obtain baseline ophthalmology exams and renal ultrasounds and then periodically during treatment.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Alexion Pharmaceuticals

Analysis: There were several studies performed to assess the safety and efficacy of Strensiq®. Study 1 was a small (N=11) 24 week prospective, single-arm study that included subjects aged 3 weeks to 39.5 months diagnosed with severe perinatal/infantile-onset HPP. Ten out of the 11 completed the study and continued treatment into the extension phase. Study 2 was a prospective open-label study (N=59) that included subjects aged 1 day to 78 months with perinatal/infantile-onset HPP. Survival and invasive ventilation-free survival were compared in Strensiq®-treated patients (Study 1 and 2) to a historical cohort of untreated patients with similar clinical characteristics. Results are shown in the table below.

	Strensiq®	Historical Controls
Survival		
N	68	48
Alive at point of last contact	91%	27%
Hazard Ratio	0.14	
Kaplan-Meier estimate & alive at age 1 year (week 48)	97%	42%
Invasive Ventilation-Free Survival		
N	54	48
Alive & Not on ventilation at point of last contact	85%	25%
Hazard Ratio	0.21	
Kaplan-Meier estimate of Alive & not on ventilation at age 1 year (week 48)	96%	31%

In patients who needed respiratory support, 81% (N=21/26) of the treated patients survived through their last assessment as compared with 5% (N=1/20) of historical controls.

In addition, radiographs were reviewed to assess HPP-related rickets, using the Radiographic Global Impression of Change (RGI-C) scale. Results included 64 subjects from Study 1 and 2, as well as 4 patients from Study 3, and patients having a minimum RGI-C score of +2 were defined as a responder. At the last assessment, 74% were rated as RGI-C responders in Strensiq®-treated patients, but comparative data was not available for historical controls.

Height and growth were measured by z-scores and are included in the table below.

	Height Z-score				Weight Z-score			
	Baseline		Last Assessment		Baseline		Last Assessment	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
Studies 1 &2 (N=68)	-3.3	-10.1, 0.9	-2.9	-10.6, 0.4	-3.2	-23.8, 0	-2.4	-20.9, 1.1
Study 3 (N=4)	-2.6	-6.6, -0.7	-1.5	-5.8, 0.4	-2.5	-8.2, -1.0	-1.5	-5.4, 0.5

Study 3 was a small prospective, open-label, 24-week study that included juvenile-onset HPP patients (N=8) and perinatal/infantile-onset HPP patients (N=5). All with juvenile-onset HPP entered the extension study and were treated for at least 48 months. Height and weight measurements (as measured by z-scores) with Strensiq®-treated subjects were compared with historical control/untreated subjects (N=32). Results are illustrated in the following table.

	Height Z-score				Weight Z-score			
	Baseline		Last Assessment		Baseline		Last Assessment	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
Strensiq® (N=8)	-1.5	-3.8, 0	-0.9	-2,0	-1.1	-3.5, 2.3	0	-1.3, 2.2
Control (N=32)	-1.1	-4.9, 2.6	-1.1	-4.9, 1.8	-1.2	-5, 2.1	-1	-5.7, 2.1

Radiographs were assessed using the RGI-C scale. All 8 juvenile-onset HPP patients were rated as responders by month 54 of treatment. At last assessment, 6% of control patients were rated as responders. Gait was also assessed, using a modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale at 6 month intervals out to 36 months. Mobility was assessed using the 6 Minute Walk Test (6MWT) in 7 of the 8 subjects. Step length improved by at least 1 point in either foot in 6 out of 8 Strensiq® treated patients as compared to 1 out of 6 in the control group. The proportion that had 6MWT percent predicted values within normal range increased from 0 out of 8 patients at baseline to 6 out of 6 patients by month 48. In addition, all 6 were able to walk longer distances as compared to baseline.

Place in Therapy: Per the National Library of Medicine/National Institutes of Health, hypophosphatasia (HPP) is "…an inherited disorder that affects the development of bones and teeth. This condition disrupts the mineralization process, in which minerals such as calcium and phosphorus are deposited in developing bones and teeth."[2] While this is a rare disease (birth prevalence of severe hypophosphatasia estimated to be 1/100,000 in the US),[2] Strensiq® is the first agent to treat the underlying cause of HPP.[3]

It is recommended that Strensiq® remain non-preferred and require prior authorization to verify diagnosis.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1]Strensiq [package insert]. Cheshire, CT: Alexion Pharmaceuticals, Inc; 2015.
[2] National Library of Medicine/National Institutes of Health. Hypophosphatasia. Website: http://ghr.nlm.nih.gov/condition/hypophosphatasia. Accessed January 2016.
[3]Strensiq. Website: http://alexion.com/Products/Strensiq. Accessed January 2016.