CENTER FOR DRUG EVALUATION AND RESEARCH

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	October 21, 2015
Reviewer(s):	Jasminder Kumar, PharmD Division of Risk Management (DRISK)
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D., DRISK
Deputy Division Director:	Reema Mehta, Pharm.D., M.P.H., DRISK
Subject:	Review evaluates if a REMS is needed for Strensiq
Drug Name:	Strensiq (asfotase alfa)
Therapeutic Class:	Long-term human tissue non-specific alkaline phosphatase enzyme replacement
Dosage form and route:	40mg/mL, 100mg/mL aqueous solution for subcutaneous administration
Application Type/Number:	BLA 125513
Applicant/Sponsor:	Alexion Pharmaceuticals, Inc.
OSE RCM #:	2015-23

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Reference ID: 3836524

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1 INTRODUCTION

The purpose of this review is to provide the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Strensiq (asfotase alfa). A biologic license application (BLA 125513) for Strensiq was received by the Division of Gastroenterology and Inborn Errors Products (DGIEP) from Alexion Pharmaceuticals, Inc. on December 23, 2014. The Sponsor did not submit a proposed REMS or risk management plan.

1.1 PRODUCT BACKGROUND

Strensiq is a human recombinant fusion protein made from the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), the human immunoglobulin G1 Fc domain, and a deca-aspartate peptide, used as a bone targeting domain. Therefore, Strensiq is a function protein that allows targeted enzyme replacement of inborn TNSALP deficiency. Replacement of the TNSALP enzyme normalizes the enzyme substrate levels, improving bone mineralization, physical function and growth. The Sponsor's proposed indication for Strensiq is (b) (4) for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP). Strensiq is a first-in-class bone-targeted enzyme replacement therapy designed to address the underlying cause of HPP, a deficiency of TNSALP activity.

The proposed dosing regimen for Strensiq is 6mg/kg of body weight per week administered subcutaneously as a dosage regimen 2mg/kg three times per week, or 1mg/kg six times per week. The dose of Strensiq may be increased up to 9mg/kg per week administered subcutaneously as 3mg/kg three times per week. The maximum recommended volume of subcutaneous injection is 1ml per injection.

1.2 DISEASE BACKGROUND

HPP is a rare, serious, and potentially fatal, genetic disorder caused by loss-of-function mutations(s) in the gene encoding TNSALP. TNSALP enzyme deficiency leads to elevations in several TNSALP substrates, which subsequently inhibits bone mineralization and causes an accumulation of unmineralized bone matrix. This can lead to respiratory failure when HPP affects the rib bones, which is the most frequent cause of death in infants with the disease, and deformities of other bones and teeth. In addition, neurologic, renal, and muscular/rheumatologic complications may occur. At least six clinical forms of HPP are currently recognized: perinatal lethal, infantile, childhood, adult, odontohypophosphatasia, and a rare benign prenatal form. However, these clinical subtypes generally overlap.[1]

The severity of disease is often inversely related to the age at onset although devastating skeletal and other systemic consequences can present at any age. In its most severe form, HPP may cause death in utero or in early infancy, with a nearly 100% mortality rate. Clinical signs and symptoms seen in perinatal-onset HPP include hypomineralization, long bone deformity, apnea, fractures, Vitamin B6-responsive seizures, and stillbirth. Infantile-onset HPP presents within the

[1] Mohn A, De Leonibus C, de Giorgis T, Mornet E, Chiarelli F. Hypophosphatasia in a child with widened anterior fontanelle: lessons learned from late diagnosis and incorrect treatment. *Acta Paediatr*. 2011;100(7):e43-e46.

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first 6 months of life and has a 50% mortality rate. It is characterized by rachitic deformities, premature tooth loss, and the presence of an open fontanelle. Childhood-onset HPP manifests from age 6 months to 18 years, and its symptoms include chronic muscle/bone pain, muscle weakness, short stature, and skeletal deformities.[2]

There is currently limited data detailing the incidence and prevalence of HPP. The incidence in the United States is about 1 in 100,000 live births; about 1 in 300 adults is a carrier. HPP primarily occurs in Caucasians but has been observed in Japanese, Hispanic, and Native American Populations; HPP is very rare among the black population.[3] It currently affects fewer than 200,000 people in the U.S. The phenotypic presentation of hypophosphatasia is extremely variable. At its worst extreme, it can present as a stillborn without dentition or calcified bones. At its mildest, hypophosphatasia can present in middle age with premature loss of teeth, foot pain (due to metatarsal stress fractures), thigh pain (due to femoral pseudofractures), or arthritis (due to chondrocalcinosis). It may also cause other systemic effects including inadequate respiratory function, seizures, and nephrocalcinosis.[4]

Management oh HPP is focused on supportive therapy to minimize complications of the disease. In infantile-onset HPP, seizures may respond to Vitamin B6. A neurosurgeon may be consulted to monitor for craniosynostosis, which may require surgical intervention to release intracranial pressure. Preventive dental care is universally-recommended at any age, regardless of whether or not an underlying condition has presented, to preserve primary dentition. Pain relievers such as NSAIDs, orthotic supports, and internal fixation may also be used as appropriate. Low impact physical activity and exercise, supervised by a physician, may improve overall bone health.[5] However, there are currently no products FDA-approved for the treatment of HPP.

1.3 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 125513 relevant to this review:

September 12, 2008: The Sponsor was granted Orphan Drug Designation.

May 14, 2009: The Sponsor was granted Fast Track designation.

May 21, 2013: The Sponsor was granted Breakthrough Therapy Designation.

March 31, 2014: The Sponsor submitted the first part (Wave 1) of the rolling submission for Strensiq.

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[2] Mohn A, De Leonibus C, de Giorgis T, Mornet E, Chiarelli F. Hypophosphatasia in a child with widened anterior fontanelle: lessons learned from late diagnosis and incorrect treatment. Acta Paediatr. 2011;100(7):e43-e46.

[3] Simmons JH. Best practices in: recognizing and diagnosing hypophosphatasia. Clinical Endocrinology News website. http://www.clinicalendocrinologynews.com/fileadmin/content_pdf/cen/Alexion_10_ 11_Final_Web.pdf. Published 2013. Accessed July 9, 2015.

[4] Fitzgerald, Paul A. "Endocrine Disorders." *Current Medical Diagnosis & Treatment 2015*. Eds. Maxine A. Papadakis, et al. New York, NY: McGraw-Hill, 2014. Access Medicine. Web. 6 Jul. 2015. <http://accessmedicine mhmedical.com/content.aspx?bookid=1019&Sectionid=57668618>.

[5] Mornet E, Nunes ME. Hypophosphatasia. In: Pagon RA, Bird TD, Dolan CR, Stephen K, eds. GeneReviews. Seattle, WA: University of Washington, Seattle; 1993. http://www ncbi.nlm.nih.gov/books/NBK1150/. Published November 20, 2007. Updated August 5, 2010. Accessed July 9, 2015

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June 30, 2014: The Sponsor submitted the second part (Wave 2) of the rolling submission for Strensiq.

December 23, 2014: The Sponsor submitted the third and final part (Wave 3) of the rolling submission for Strensiq. At this time, the Sponsor requested a Priority Review.

February 27, 2015: The Agency issued a Filing Communication, informing the Sponsor that there were no filing review issues identified. The review classification for this application was determined to be Priority.

March 20, 2015: The Sponsor submitted a major amendment to the application.

April 10, 2015: The Agency extended the goal day by three months to provide time for a full review of the major amendment submitted by the Sponsor on March 20, 2015.

July 14, 2015: A Mid-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that based on their currently available data a REMS was not needed for Strensiq.

September 2, 2015: A Late-Cycle Meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that no issues related to risk management have been identified to date.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Alexion Pharmaceuticals, Inc. Summary of Clinical Safety for Strensiq (asfotase alfa), received December 23, 2014.
- Alexion Pharmaceuticals, Inc. Summary of Clinical Efficacy for Strensiq (asfotase alfa), received December 23, 2014.
- Alexion Pharmaceuticals, Inc. Proposed Prescribing Information for Strensiq (asfotase alfa), received December 23, 2014, updated March 13, 2015 and August 14, 2015.
- Alexion Pharmaceuticals, Inc. 120-Day Safety Update Report for Strensiq (asfotase alfa), received April 17, 2015.
- Vali BP, Chen YF. Division of Biometrics III. Statistical Review and Evaluation for Strensiq (asfotase alfa), dated September 19, 2015.
- Epps C. DGIEP. Clinical Review for Strensiq (asfotase alfa), dated October 21, 2015.

3 REVIEW FINDINGS FOR STRENSIQ

3.1 OVERVIEW OF CLINICAL PROGRAM

The safety and efficacy of Strensiq was evaluated from results of 3 pivotal trials, including 2 ongoing extension studies, and 1 supportive trial. These studies were conducted in 102 HPP patients who received treatment for up to 240 weeks. Subjects ranged in age in treatment initiation from 1 day to 66 years. The overall analysis set included a total of 102 patients who were treated, including 79 with infantile-onset HPP, 20 with juvenile-onset HPP, 2 with adult-onset, and 1 HPP patient with time of disease onset not known. However, the Sponsor did not pursue treatment of the adult onset patient population in this application.

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All pivotal studies were open-label in design because of the absence of any alternative disease-modifying treatments. No placebo or active comparator controls were employed in the clinical trials. However, natural history studies were conducted in patients with HPP to permit comparative analyses of Strensiq-treated versus non-treated patients for the demonstration of efficacy. There were 3 non-interventional natural history studies that were used to support the proposed indication for Strensiq. These natural history studies served as historical controls for the primary efficacy analysis. 86 patients from the natural history studies were used for comparative analysis.

The clinical studies in the Strensiq development program include:

- *Pivotal open label studies*
    - **ENB-002-08** (and its ongoing extension trial, **ENB-003-08**): enrolled patients ≤3 years of age with onset of symptoms <5 months of age (perinatal/infantile-onset population)
    - **ENB-010-10** (ongoing): enrolled patients ≤5 years of age with onset of symptoms <6 months of age (perinatal/infantile-onset population)
    - **ENB-006-09** (and its ongoing extension trial, **ENB-008-10**): enrolled patients 5 through 12 years of age with onset of symptoms ≤12 years of age (perinatal/infantile- and juvenile-onset population)
- *Open-label, supportive study*
    - **ENB-009-10** (ongoing): enrolled adolescent and adult patients (12 through 66 years of age) regardless of age of symptoms onset (perinatal/infantile-, juvenile-, or adult-onset)
- *Comparative, retrospective, non-interventional, natural history studies*
    - **ENB-011-10**: data abstracted from medical records of children up to 5 years of age and served as the control group for comparative analyses of survival and invasive ventilator-free survival in patients with severe perinatal/infantile-onset HPP who were treated with Strensiq in Studies ENB-002-08/ENB-003-08 and ENB-010-10.
    - **ALX-HPP-502**: data abstracted from medical records of qualifying children with baseline and subsequent data available during childhood/early adolescence to serve as the control group for comparative analysis of bone structure and growth in juvenile-onset patients treated with Strensiq in Studies ENB-006-09/ENB-008-10.
        - **ALX-HPP-502s**: single-center sub-study in which data for additional functional measures were abstracted from medical records and videos from a longitudinal national history database to characterize gait. This study served as the control group for comparative analyses of gait in juvenile-onset patients treated with Strensiq in Studies ENB-006-09/ENB-008-10.

In addition, as of November 30, 2014, 16 patients received treatment with Strensiq for HPP under compassionate use programs in the following countries: Japan, United Kingdom, Germany, Australia, The Netherlands, and South Africa.

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3.2 SUMMARY OF EFFICACY[6]

Data from trials ENB-002-08/ENB-003-08 and ENB-010-10, compared to natural history cohorts, supported the proposed use of Strensiq in the perinatal /infantile-onset HPP population. The primary efficacy outcome was overall survival with ventilator-free survival as a key secondary endpoint. The natural history studies showed survival rates were higher for patients born in or after the year 2000, but survival rates were low regardless of diagnosis period. There was a statistically significant survival improvement ($p<0.0001$) in patients treated with Strensiq. Similar results were seen for ventilator-free survival, with a rate of 96% for Strensiq-treated patients compared to 31% for historical control patients. In addition, growth and radiographic data results showed patients had improvements in height, weight, and healing of rickets. In Study ENB-002-08 and Study ENB-010-10, improvement in rickets severity on skeletal radiographs, measured by Radiographic Global Impression of Change (RGI-C) at Week 24, showed significant change from baseline with a median RGI-C score of 2 and 1.67 ($p=0.0039$, $p<0.001$, respectively). However, RGI-C scores for historical controls are not available for comparison. Improvements in the skeletal manifestations of HPP were accompanied by benefits in respiratory status, growth, and motor function for both studies.

Data from open-label trial (ENB-006-09/ENB-008-10) supported the juvenile-onset population. For patients with juvenile-onset HPP, an integrated analysis was performed for the natural history studies. The primary endpoint was comparison of mobility/gait with historical controls as assess during performance-oriented mobility-gait (mPOMA-G) scores. In historical controls, substantial and persistent gait defects were identified in all studied patients. Patients treated with Strensiq demonstrated significant improvements in ambulation and gait as measure by the rate of change per year in mPOMA-G score from baseline to last assessment (2.25/year), compared with historical controls (0.37/year) ($p=0.0303$). However, the clinical review team did not consider the primary efficacy analysis for the juvenile-onset population- change in gait- to be robust from either a statistical or a clinical perspective. The Sponsor's use of the mPOMA-G tool, one that is not validated, is one of the factors that limited the team's analysis. In addition, the analysis was decided post-hoc and collected after results for clinical trials were already known. Instead the totality of evidence provides evidence to support an efficacy claim for the juvenile-onset population.[7]

Specifically, study ENB-006-09 showed statistically significant improvements relative to historical control patients in rickets severity, as measured by RGI-C, as early as Week 24 ($p=0.0007$). There was also reduced osteoid thickness and osteoid volume. Mean change from baseline to Week 24 was 3.858 µm ($p=0.0097$) for osteoid thickness indicative of osteomalacia. Mean osteoid volume was 13.753% with a mean change from baseline to Week 24 of 4.225% ($p=0.0789$). Measurable gains occurred in growth, ambulation, strength, speed and agility, as measure by the 6MWT and the BOT-2.

In addition, study ENB-009-10, the supportive study, showed the change in plasma PPi level from baseline Week 24 for the Strensiq group was -2.218 µM as compared to the control group,

[6] All presented p-values within this review are considered supportive based on determination by the Agency's statistical review and evaluation: Vali BP, Chen YF. Division of Biometrics III. Statistical Review and Evaluation for Strensiq (asfotase alfa), dated September 19, 2015.

[7] Epps C. DGIEP. Clinical Review for Strensiq, BLA 125513, dated October 21, 2015.

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0.106 µM ($p<0.05$). Plasma PLP levels for the Strensiq group (mean changes -397.72) also had statistically significant reductions ($p=0.0285$) compared to the control group (mean change 3.13 ng/mL).

ALX-HPP-502 showed there were no significant changes in rickets severity or growth over the time period of 5 to 15 years of age evaluated, providing useful clinical data to compare with results observed in the active-treatment studies. Strensiq treatment was associated with statistically significant improvement in RGI-C at Week 24, with a median score of 2.00, corresponding with "substantial" heading as compared to a change of 0.33 (no healing) for untreated historical control patients ($p<0.001$).

3.3 SUMMARY OF SAFETY CONCERNS

Data from 6 ongoing or completed clinical studies (ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10, and ENB-009-10) were included in the integrated safety analyses. The integrated safety analyses (n=102) included 79 perinatal/infantile-onsite HPP patients, 20 patients with juvenile-onset HPP, 2 patients with adult-onset HPP, and 1 patient with undetermined disease onset. For a comprehensive safety evaluation, data from the 120 Day Safety Update Report, submitted on April 17, 2015 was also evaluated, which included 16 patients treated under compassionate use programs.

Common Adverse events

All patients included in the integrated safety analyses experienced one or more treatment emergent adverse event (TEAE). A total of 3676 TEAEs were reported for these patients. There were 7 TEAEs in 5 patients that led to discontinuation of Strensiq treatment and study withdrawal. Of the reported TEAEs, 69% were considered by the investigator to be not related to treatment with Strensiq. Additionally, of the total TEAEs, 75% were mild and 5% were severe. Of the TEAEs considered related to study drug by the investigator, 90% were injection-site reactions (ISR). In addition, 47% of TEAEs occurred during the first 24 weeks of treatment. The overall frequency of TEAEs, including SAEs, decreased with continued treatment with Strensiq.

3.3.1 Serious Adverse Events (SAEs)

There were a total of ten deaths reported in patients treated with Strensiq; seven reported in clinical studies for Strensiq and three in patients treated in compassionate use programs. All deaths were attributed to HPP-related disease complications. The clinical reviewer agreed with investigator's assessment.

A total of 274 nonfatal SAEs were reported the integrated safety analyses in 48 patients; 94% of the events were considered not related to Strensiq by the Investigator. Of the nonfatal SAEs that were considered related to Strensiq treatment by the Investigator, 10 events occurred in infantile-onset patients (n=7) and 6 events occurred in one juvenile-onset HPP patient (n=1). The events reported among these 8 patients included the following: chronic hepatitis (n=1), craniosynostosis (n=2), conductive deafness (n=1), oral hypoesthesia (n=1), extremity pain (n=1), chills (n=4), headache (n=1), injection site reaction (n=2), pyrexia (n=1), injection site abscess (n=1), and dosing error (n=1). The clinical reviewer agreed with the investigator regarding the aforementioned SAEs and their relation to Strensiq treatment with the exception of

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craniosynostosis; the clinical reviewer concluded there was insufficient evidence to attribute a relation for craniosynostosis.[8]

3.3.2 Adverse Events of Special Interest (AESIs)

AESIs included IAR, including hypersensitivity reactions, and ectopic calcification.

Although the Sponsor reported no events that were associated with anaphylaxis following SC administration of Strensiq, the clinical reviewer's analysis revealed one patient that experienced an anaphylactic reaction using the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis network criteria for anaphylaxis. In addition, of 98 patients with antibody testing results, 76 patients (78%) developed anti-drug antibody (ADA) titers to Strensiq. Since formation of ADA can result in side effects such as anaphylactic shock, the clinical reviewer determined that long-term immunogenicity safety data, including incidence rates of anaphylaxis is needed.[7]

Twenty-five patients experienced a total of 29 events suggestive of ectopic calcification, including events reported in ≥2 patients: deposit eye, conjunctival deposit and nephrocalcinosis, and corneal deposit. All events were mild or moderate, but one case of nephrocalcinosis was considered to be related to Strensiq by the Investigator. All events were asymptomatic with no changes in visual acuity. Although ectopic calcifications including nephrocalcinosis, conjunctival calcifications, and band keratopathy, are known complications of HPP[9], the clinical reviewer notes that treatment with Strensiq may cause the potential formation of ectopic calcifications in other tissues as inorganic phosphate released through enzymatic activity binds with calcium to form hydroxyapatite crystal.[7,10] In addition, no data was available on the prevalence of conjunctival calcifications or band keratopathy from the natural history studies. The clinical reviewer concluded there was not enough information for the ectopic calcifications described to determine whether they represent known disease complications or new safety signals and recommends additional information on ectopic calcification events be collected as a post-marketing requirement (PMR).

4 DISCUSSION

Based on results of the clinical program, Strensiq was found to be efficacious with an acceptable safety profile for use as an enzyme-replacement therapy for patients with perinatal/infantile- and juvenile-onset HPP. The AESIs associated with Strensiq include IAR, including hypersensitivity reactions and ectopic calcifications. .

Hypersensitivity, including anaphylaxis, is a potential adverse reaction for Strensiq since this reaction is associated with other protein products; however, only one case of anaphylaxis with Strensiq was reported. The clinical development program only included 102 patients; based on the potential risk associated with protein products, a higher incidence of anaphylaxis cases may

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[8] Epps C. DGIEP. Clinical Review for Strensiq, BLA 125513, dated October 21, 2015.

[9] Lessell S, Norton EW. Band keratopathy and conjunctival calcification in hypophosphatasia. *Arch Ophthalmol*. 1964 Apr;71:497-9.

[10] Giachelli CM. Ectopic Calcification: Gathering Hard Facts about Soft Tissue Mineralization. *Am J Pathol*. 1999 Mar; 154(3): 671–675.

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occur in a postmarketing setting. To determine the long-term impact of immunogenicity on the safety profile for Strensiq, DGIEP recommends a post marketing commitment to obtain this information. With regards to ectopic calcification, a known complication of HPP, there was insufficient evidence to determine whether events were due to known disease complications or new safety signals. As a result, the Division recommends obtaining information about ectopic calcifications via a PMR, as well.

In addition, the overall frequency of TEAEs, including SAEs, decreased with continued treatment with Strensiq. Many of the AEs seen with Strensiq were associated with the disease state itself. Further, prescribers will likely be specialists, familiar with the disease state and its need for continual monitoring.

Therefore, based on the currently available data, DRISK does not recommend a REMS as necessary to ensure the benefits of Strensiq outweigh the risks. HPP is a rare, orphan disease that currently has no cure. Without treatment, HPP can cause clinical sequelae including: skeletal, respiratory, neurologic, renal, and muscular/rheumatic. The Agency has designated Strensiq as an orphan and breakthrough therapy, and there are no Boxed Warnings under consideration. The proposed Warnings and Precautions section of the Package Insert Labeling for Strensiq includes monitoring patients for systemic hypersensitivity reactions, injection site lipodystrophy, and ectopic calcifications.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Strensiq. Based on the currently available data, the benefit-risk profile for Strensiq is acceptable for (b) (4) therapy in patients with perinatal/infantile- and juvenile-onset HPP and a REMS is not warranted at this time.

Should DGIEP have any concerns or questions, or feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

JASMINDER N KUMAR
10/21/2015

REEMA J MEHTA
10/21/2015
I concur with the conclusion.