Authorization with conditions of STRENSIQ™ (asfotase alfa), indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia

August 13, 2015

Dear Health Care Professional:

Alexion Pharma Canada is pleased to announce that Health Canada has issued a Notice of Compliance with Conditions under the Notice of Compliance with Conditions (NOC/c) policy for Strensiq™ (asfotase alfa), Parenteral Solution (40 mg/mL and 100 mg/mL) indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia.

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for Strensiq, to reflect the promising nature of the clinical data of Strensiq in patients with this serious disease and the need for further follow-up to verify the clinical benefit. The safety profile of Strensiq has been found to be acceptable based on the current benefit/risk assessment. As part of its conditions, Alexion has undertaken to provide Health Canada with additional data by submitting final Clinical Study Reports from the following ongoing studies:

- ENB-006-09 entitled "A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Historical Control Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Children with Hypophosphatasia (HPP)".

- ENB-008-10 entitled "Extension Study of Protocol ENB-006-09 Evaluating the Long-Term Safety and Efficacy of ENB-0040 (Human Recombinant Tissue- Nonspecific Alkaline Phosphatase Fusion Protein) in Children with HPP".

In addition, these studies will provide efficacy and safety data in patients who will be
reaching 13 to 18 years of age by the time the study is completed.

- **ENB-010-10** entitled: "An Open-Label, Multicenter, Multinational Study of the Safety, Efficacy, and Pharmacokinetics of Asfotase Alfa (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in Infants and Children 5 Years of Age with HPP".

- **ENB-009-10** entitled: "A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Concurrent Control Study of the Safety, Efficacy, and Pharmacokinetics of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Adolescents and Adults with HPP".

- **ENB-002-008** entitled: "A multicenter, open-label study of the safety, tolerability, and pharmacology of Study ENB-0040 (Enobia's human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in up to 10 severely affected patients with infantile HPP".

- **ENB-003-08** entitled: "Extension study of ENB-0040 (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in severely affected infants and young children with HPP".

- In addition to the above listed ongoing Clinical Studies, Alexion has committed to conduct a PK/PD study of asfotase alfa in adult patients with HPP in order to evaluate pharmacokinetic profile of asfotase alfa in adults at the authorized dose, to demonstrate the dose response on plasma PPI and PLP and to explore evidence of clinical benefit. The final Clinical Study Report will be submitted to Health Canada.

**Indications and Clinical Use:**
Strensiq is indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia. Patients should be advised about the conditional market authorization for this indication.

**Action and Clinical Pharmacology:**
Strensiq is a fusion protein that combines the catalytic human tissue non-specific alkaline phosphatase (TNSALP) enzyme domain and a bone targeting anchor, which allows targeted enzyme replacement of TNSALP deficiency in HPP patients. Restoring TNSALP enzyme activity in HPP patients normalizes the levels of TNSALP enzyme substrates, improve bone mineralization, and bone health.

**Adverse Reactions:**
Systemic injection-associated reactions (IARs), defined as any related adverse event occurring during the injection or until the end of the injection day, are possible with administration of exogenous proteins. No reports of anaphylaxis or anaphylactoid reactions have been noted following treatment with Strensiq in any clinical trials.

Administration of Strensiq may result in local injection site reactions (ISRs), including, but not limited to, erythema, rash, discoloration, pruritus, pain, papule, nodule, atrophy at the injection site. Rotation of injection sites usually helps to effectively manage these reactions. These reactions have been generally assessed as non-serious, mild to moderate in severity and self-
limiting. One patient treated in clinical trials experienced a severe ISR of injection site
discolouration and withdrew from the trial.

Strensiq administration should be interrupted in any patient experiencing severe injection
reactions and appropriate medical therapy administered.

In clinical trials, 68 paediatric-onset patients (age 1 day to 66 years) were treated with Strensiq,
with majority for more than two years (range 0.1 to 260.9 weeks). The most common adverse
reactions observed were ISRs and IARs. The majority of these reactions were non-serious, mild
to moderate in intensity. Serious adverse reactions of IARs were reported in 2 patients with no
discontinuation of Strensiq treatment: in 1 patient with infantile-onset reported as fever and
chills, and in 1 patient with juvenile-onset HPP reported as hypoaesthesia oral, pain in extremity,
chills, and headache.

**Drug-Drug Interactions:**
Interactions with other drugs have not been established.

**Dosage and Administration:**

**Recommended Dose and Dosage Adjustment**
Recommended dosage regimen of Strensiq is 2 mg/kg of body weight administered
subcutaneously three times per week, or a dosage regimen of 1 mg/kg of body weight
administered six times per week. The maximum volume of subcutaneous injection is 1 mL per
injection.

**Administration**
Strensiq should not be administered intravenously or intramuscularly.

Strensiq should be administered as subcutaneous injections. The maximum volume of
medication per injection should not exceed 1 millilitre (mL) per single injection site. If more
than 1 mL is required, multiple injections may be administered at the same time at different
injection sites.

Injections sites should be rotated and carefully monitored for signs of potential reactions.
Strensiq should be administered using sterile disposable syringes and injection needles. The
syringes should be of small enough volume that the prescribed dose can be withdrawn from the
vial with reasonable accuracy.

For the complete prescribing information and information available for the patients/caregivers,
please consult the Strensiq Product Monograph. The Product Monograph can be obtained by
contacting Alexion at 1 866 393-1188 ext 10401.

Should you have medical enquiries regarding Strensiq, please contact our Medical Information
Department at 1 866 393-1188 ext 10412.

*original signed by*

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Vaughan, Ontario L4K 0G6

**Reporting Suspected Side Effects**
Canada Vigilance Program
Marketed Health Products Directorate
Health Products and Food Branch
HEALTH CANADA
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
K1A 0K9
Telephone: 613-957-0337 or Facsimile: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Facsimile: 1-866-678-6789
Email: CanadaVigilance@hc-sc.gc.ca

The [Adverse Reaction Reporting Form](#) and the [Adverse Reaction Guidelines](#) can be found on the Health Canada website or in [The Canadian Compendium of Pharmaceuticals and Specialties](#).

For other health product inquiries related to this communication, please contact Health Canada at:
Biologics and Genetic Therapies Canada
Therapeutic Products Directorate
Email: bgtd_ora@hc-sc.gc.ca
Telephone: 613-957-1722
Facsimile: 613-946-9520