PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**STRENSIQ®**

(asfotase alfa)

Solution for Injection 40 mg/mL & 100 mg/mL

Enzyme Replacement Therapy

ATC code: A16AB13

STRENSIQ® (asfotase alfa), indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for STRENSIQ® please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

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Date of Initial Approval:
August 14, 2015

Date of Revision:
May 16, 2019

Control No: 224481

Date of Approval: May 22, 2019

This product has been authorized under the Notice of Compliance with Conditions (NOC/c)

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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Pr STRENSIQ®

(asfotase alfa)

PART I: HEALTH PROFESSIONAL INFORMATION

STRENSIQ® (asfotase alfa), indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for STRENSIQ® please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Concentration	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous Injection	Solution for Injection 40 mg/mL & 100 mg/mL	Sodium (23 mg) per vial *For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

Strensiq (asfotase alfa) is a soluble glycoprotein of 726 amino acids made from the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), the human immunoglobulin G_1 Fc domain and a deca-aspartate peptide used as a bone targeting domain[1,2]. Strensiq is intended for subcutaneous administration. It is supplied as a sterile, nonpyrogenic, clear, colourless, aqueous solution containing 40 mg/mL or 100 mg/mL asfotase alfa, 25 mM sodium phosphate, and 150 mM sodium chloride at a pH between 7.2 and 7.6, inclusive, supplied in a single-use glass vial intended for subcutaneous administration. Strensiq does not contain any preservatives.

NOC/c INDICATIONS AND CLINICAL USE

Strensiq (asfotase alfa) is indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia.

Treatment with Strensiq should be initiated by a physician with experience in the management of patients with metabolic bone disorders.

Geriatrics (> 65 years of age): The safety and efficacy of Strensiq in patients older than 65 years have not been evaluated (see subsection Special Populations, under section **WARNINGS AND PRECAUTIONS**).

Paediatrics (0 - 18 years of age):
See subsection *Special Populations*, under section **WARNINGS AND PRECAUTIONS**.

NOC/c CONTRAINDICATIONS

Strensiq is contraindicated in patients who are hypersensitive to the active substance, or to any of the excipients in the formulation. For a complete listing, see section **DOSAGE FORMS, COMPOSITION AND PACKAGING,** of the product monograph.

NOC/c WARNINGS AND PRECAUTIONS

General

Hypersensitivity

Hypersensitivity reactions have been reported in Strensiq-treated patients including signs and symptoms consistent with anaphylaxis. These symptoms included difficulty breathing, choking sensation, nausea, periorbital edema, and dizziness. The reactions have occurred within minutes after subcutaneous administration of Strensiq and can occur in patients on treatment for more than one year. Other hypersensitivity reactions included vomiting, fever, headache, flushing, irritability, chills, skin erythema, rash, pruritus, and oral hypoesthesia.

If these reactions occur, immediate discontinuation of Strensiq treatment is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment should be observed.

Lipodystrophy

Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with Strensiq in clinical trials (see **ADVERSE REACTIONS** section). Advise patients to follow proper injection technique and to rotate injection sites (see **DOSAGE AND ADMINISTRATION** section).

Injection 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 (See section **ADVERSE REACTIONS**).

Administration of Strensiq may result in local injection site reactions (ISRs), including, but not limited to, erythema, rash, discolouration, 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.

Treatment Discontinuation

Possible Risk of Hypercalcemia upon Discontinuation of Strensiq
Patients with HPP are known to experience hypercalcemia as well as seizures as a result of their underlying disease. While serum calcium in patients with HPP who discontinue Strensiq has not been systemically studied, a review of non-clinical data and post-marketing reports suggests that there is insufficient evidence to conclude that discontinuing Strensiq leads to a greater risk of hypercalcemia compared to that expected due to the underlying disease. Patients should be advised and monitored for the re-emergence of their HPP symptoms, including hypercalcemia, should discontinuation of therapy be necessary.

Carcinogenesis and Mutagenesis
Carcinogenesis and mutagenesis studies have not been performed. There is no evidence to suggest that the use of Strensiq is associated with carcinogenesis (See subsection **Preclinical Safety Data** under section **TOXICOLOGY**).

Cardiovascular
The safety and efficacy of Strensiq have not been studied in patients with cardiovascular manifestations.

Dependence/Tolerance
There is no evidence to suggest that the use of Strensiq is associated with drug abuse or dependence.

Disproportionate weight gain
Patients may display disproportionate weight increase. Dietary supervision is recommended.

Ear/Nose/Throat
There were no serious Ear/Nose/Throat adverse reactions.

Ectopic Calcification
Patients with HPP are at increased risk for developing 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.

In clinical trials with Strensiq, 14 cases (14%) of ectopic calcification of the eye including the cornea and conjunctiva, and the kidneys (nephrocalcinosis) were reported.

There was insufficient information to determine whether or not 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.

Endocrine and Metabolism
There were no serious endocrine or metabolic adverse reactions.

Gastrointestinal
Hypoaesthesia oral and Nausea were commonly reported adverse reactions.

Genitourinary
There were no serious genitourinary adverse reactions.

Hematologic
In clinical trials, hot flush and increased tendency to bruise were observed.

Hepatic/Biliary/Pancreatic
Hepatic function, measured as serum alanine transaminase (ALT) and serum aspartate transaminase (AST), was investigated in the population pharmacokinetic model and did not reveal an impact of hepatic function on asfotase alfa clearance.

Hepatic Impairment
The safety and efficacy of Strensiq was not evaluated in patients with hepatic impairment.

Immune
As with all therapeutic proteins, there is potential for immunogenicity. During clinical trials, anti-drug antibodies have been detected in patients receiving treatment with Strensiq using an electrochemiluminescent (ECL) immunoassay. Antibody positive samples were tested to determine the presence of neutralizing antibodies based on *in vitro* inhibition of the catalytic activity of Strensiq. Among 69 hypophosphatasia (HPP) patients enrolled in the clinical trials and who have post-baseline antibody data, 56 (81.2%) tested positive for anti-drug antibodies at some time point after receiving Strensiq treatment. Among those 56 patients, 25 (44.6%) also showed the presence of neutralizing antibodies. No correlation was observed between the anti-drug antibodies titer and neutralizing antibodies (% inhibition) values. The antibody response (with or without the presence of neutralizing antibodies) was time variant in nature and is considered low based on the impact on the pharmacokinetics of asfotase alfa and the available safety and efficacy data (See subsection **Pharmacokinetics** under section **TOXICOLOGY**).

No trends in Adverse Events (AEs) based on antibody status have been observed in clinical trials.

In the post-approval setting, rare instances of inhibitory antibody activity were reported in association with decreased clinical response. In 1 case, the patient underwent desensitization and was successfully re-challenged.

Infections and Infestations
In asfotase alfa clinical studies the majority of adverse events related to infections and infestations were respiratory infections including pneumonia, upper respiratory tract infection and nasopharyngitis. They occurred primarily in patients in the infantile-onset HPP subgroup and

were usually experienced by patients <2 years of age. These types of events were not unexpected, particularly in patients with more severe manifestations of HPP.

Craniosynostosis
Craniosynostosis as a manifestation of hypophosphatasia is documented in published literature and occurred in 61.3% of patients between birth and 5 years of age in a natural history study of untreated infantile-onset hypophosphatasia patients. Craniosynostosis can lead to increased intracranial pressure. Periodic monitoring (including fundoscopy for signs of papilloedema) and prompt intervention for increased intracranial pressure is recommended in patients with infantile-onset HPP below 5 years of age.

In asfotase alfa clinical studies, adverse events of craniosynostosis (associated with increase of intracranial pressure) related to underlying disease was observed in patients < 5 years of age. There are insufficient data to establish a causal relationship between exposure to Strensiq and progression of craniosynostosis.

Peri-Operative Considerations
There is no data on continuing or discontinuing Strensiq or adjusting dose for Peri-Operative considerations.

Psychiatric
There were no serious psychiatric adverse reactions.

Renal
The safety and efficacy of Strensiq was not evaluated in patients with renal impairment.

Respiratory, Thoracic and Mediastinal Disorders
In clinical studies the majority of events of respiratory, thoracic and mediastinal disorders were reported in patients in the infantile-onset HPP subgroup, usually those patients <2 years of age, and often associated with events that reflected severe respiratory-associated manifestations of HPP including respiratory distress, respiratory disorders and dyspnea.

Sensitivity/Resistance
As with all infusions with biologic agents, there is a risk of injection reactions and anaphylaxis. (For information regarding allergic/injection reactions, see subsection **General** under section **Hypersensitivity/ Injection Reactions**).

Serum Parathyroid Hormone and Calcium
Serum parathyroid hormone concentration may increase in HPP patients administered Strensiq, most notably during the first 12 weeks of treatment. It is recommended that serum parathyroid hormone and calcium be monitored in patients treated with Strensiq. Supplements of calcium and oral vitamin D may be required.

Sexual Function/Reproduction
The safety of Strensiq during pregnancy and breastfeeding has not been established (See subsection **Pregnant Women** under section **WARNINGS AND PRECAUTIONS**).

Skin
There were no serious skin (photosensitivity, photoallergic or phototoxic) adverse reactions.

Special Populations:

Pregnant Women:
There are no studies of Strensiq in pregnant women. Pregnant and lactating women were excluded from the Strensiq clinical trials. During the trials there were no reported pregnancies. [For animal studies, see PART II, Toxicology].

Nursing Women:
It is not known whether Strensiq is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when administering Strensiq to a nursing woman.

Paediatrics (0 - 18 years of age):
The safety and efficacy of Strensiq have been studied in paediatric patients between 0-18 years of age. For further details on Patient demographics in clinical trials for hypophosphatasia, refer to Table 3 under *CLINICAL TRIALS: Study Demographics and Trial Design* section.

Geriatrics (> 65 years of age):
The safety and efficacy of Strensiq in patients older than 65 years have not been evaluated. Clinical studies of Strensiq did not include sufficient numbers (n=1) of patients aged 65 years and over.

Monitoring and Laboratory Tests
Injections sites should be rotated and carefully monitored for signs of potential reactions (See subsection **General** under section **WARNINGS AND PRECAUTIONS**).

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview
In clinical trials, 68 paediatric-onset patients (age 1 day to 66 years) were treated with Strensiq. 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.

In clinical trials, 19 of the 68 paediatric-onset patients were continuously treated with the recommended dose of 6 mg/kg/week. This represents 25.88 total patients years of exposure with a mean duration of treatment of 1.36 years (min=0.4, max=2.8).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Tabulated list of adverse reactions

Table 1 displays the adverse reactions observed from clinical trials following subcutaneous injection of Strensiq listed by system organ class and preferred term. Due to the small patient population in the clinical trials, a tabulated summary of adverse reactions reported in ≥5% of patients is presented.

Table 1: Adverse Reactions Reported in Strensiq Clinical Trials in HPP patients (age 1 day to 18 years)

System Organ Class	Adverse reaction ≥5% (Preferred Term Level)
	Infantile and Juvenile onset HPP (N=99)
General disorders and administration site conditions	Injection site reactions (ISRs)* Pyrexia (45%) Irritability (9%)
Skin and subcutaneous tissue disorders	Erythema (10%) Lipohypertrophy (5%)
Gastrointestinal disorders	Nausea (5%)
Musculoskeletal and connective tissue disorders	Pain in extremity (36%) Myalgia (7%)
Injury, poisoning and procedural complications	Contusion (16%)
Nervous system disorders	Headache (21%)

**** Preferred terms considered as ISRs are presented in section below***

Description of selected adverse reactions

Injection site reactions (ISRs):

ISRs (including injection site erythema, discolouration, pain, pruritus, macule, swelling, bruising, hypertrophy, induration, reaction, atrophy, nodule, rash, papule, haematoma, inflammation, urticarial, warmth, haemorrhage, cellulitis and mass) are the most common adverse reactions observed in approximately 73% of the patients in the clinical studies. The majority of ISRs were mild and self-limiting, and none were reported as serious adverse events. Two patients experienced ISRs that led to reductions of their Strensiq dose. The frequency of ISRs was higher in patients with juvenile-onset HPP and in patients who received injections 6 times/week (compared to 3 times/week).

Hypersensitivity
Hypersensitivity reactions include erythema/redness, pyrexia/fever, irritability, nausea, pain, rigor/chills, hypoesthesia oral, headache, flushing, and signs and symptoms consistent with anaphylaxis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via to the Canada Vigilance Program.

Abnormal Hematologic and Clinical Chemistry Findings
There were no abnormal hematology or clinical chemistry values considered as adverse drug reactions following Strensiq administration.

Post-Market Adverse Drug Reactions
There has been limited post-marketing experience with Strensiq in HPP patients.

DRUG INTERACTIONS

Overview
No drug interaction studies and no *in vitro* metabolism studies have been performed. Because asfotase alfa is a human recombinant fusion protein, it is an unlikely candidate for cytochrome P450 mediated interactions.

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

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Alkaline Phosphatase (ALP) is used as the detection reagent in many routine laboratory assays. If asfotase alfa is present in clinical laboratory samples, aberrant values could be reported.

The treating physician should inform the testing lab that the patient is treated with medication affecting the ALP levels. Alternative assays (i.e. not utilizing an ALP-conjugated reporter system) may be considered in patients treated with Strensiq.

Drug-Lifestyle Interactions
No studies on the effects on the ability to drive and use machines have been performed.

NOC/c 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.

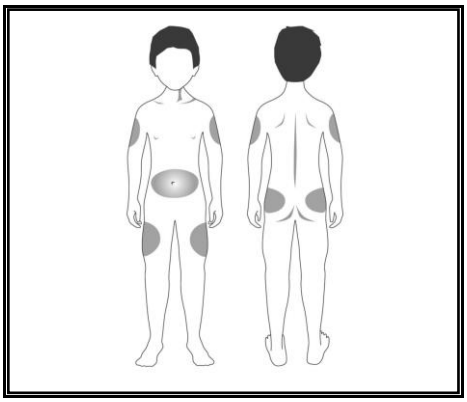
Administration
Strensiq should not be administered intravenously or intramuscularly**.**

Strensiq should be administered as subcutaneous injections. The maximum volume of medication per injection should not exceed 1 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.

Injection sites should be rotated and carefully monitored for signs of potential reactions including lipodystrophy. 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 administration of Strensiq, please read the following instructions carefully:
Each vial is for single use and should only be punctured once. Only clear and colourless to slightly yellow solution without visible signs of deterioration should be used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

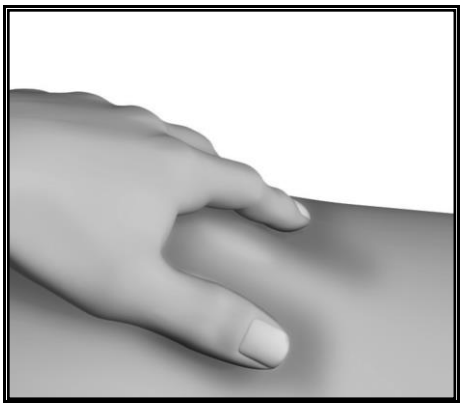
How to inject Strensiq:
Wash your hands thoroughly with soap and water.
Remove the protective cap from the Strensiq vial.
Withdraw the correct dose of Strensiq into the syringe.



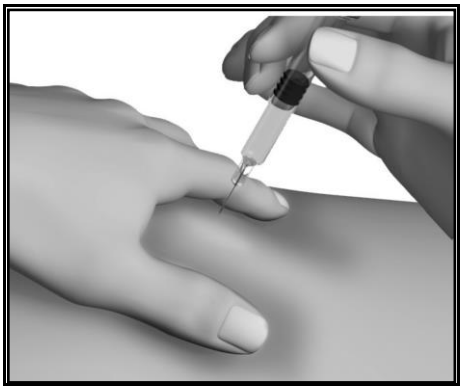
It is important to rotate Strensiq injection sites. Do not administer injections in areas that are reddened, inflamed or swollen.

Determine the injection site then, using a 60-70% alcohol-based solution (isopropyl alcohol or ethanol) on a single use or cotton-wool ball, clean the site.

NOTE: Do not use any areas in which you feel lumps, firm knots, or pain.



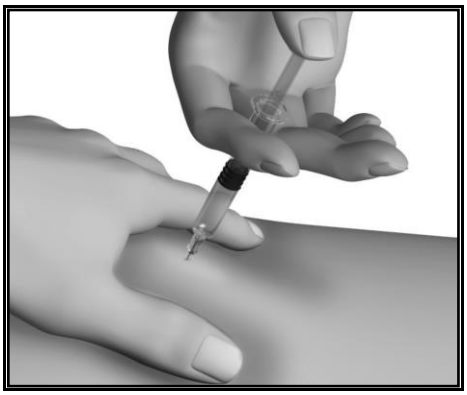
Gently pinch the skin of the chosen injection area between your thumb and index finger.



Subcutaneously administer the prescribed dose to the injection site.

Holding the syringe like a pencil or a dart, insert the needle into the raised skin so it is at an angle of between 45º and 90º to the skin surface.

For patients who have little subcutaneous fat or thin skin, a 45º angle may be preferable.



While continuing to hold the skin, push the syringe plunger to inject the medication while counting slowly to 10.
Remove the needle, release the skin fold and gently place a piece of cotton wool or gauze over the injection site for a few seconds.
This will help seal the punctured tissue and prevent any leakage.
Do not rub the injection site after injection.
Place bandage onto the injection site and properly dispose of the needle.

Reconstitution
Strensiq is a ready to use, human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein for subcutaneous administration. Therefore, Strensiq should not be reconstituted.

Missed Dose
In case of a missed dose, resume the regular schedule as soon as possible. Scheduling of subsequent doses should be determined by the treating physician and the Strensiq dosing regimen (See subsection **Recommended Dose and Dose Adjustment** under section **DOSAGE AND ADMINISTRATION**).

OVERDOSAGE

No overdose level has been determined.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Strensiq replaces the defective TNSALP enzyme.

Pharmacodynamics

In clinical trials in patients with HPP, increase in ALP was noted almost immediately after initiation of treatment with asfotase alfa. PLP and PPi levels also improved rapidly with stable reductions in the normal range by approximately 3 and 20 weeks, respectively. Subsequent improvements in clinically relevant endpoints are described in the clinical study sections.

Pharmacokinetics

Pharmacokinetic (PK) data with asfotase alfa were evaluated in a wide range of HPP patients (age 1 day to 66 years). Based on population PK analysis, asfotase alfa PK exposure increased proportionally over the studied doses of up to 28 mg/kg/wk. Table 2 provides a summary of Strensiq PK parameters.

Table 2: Summary of Strensiq Pharmacokinetic (PK) Parameters Based on Pooled PK Data

Half-Life (days) Mean ± SD	**$C_{avg, ss}$ for 2 mg/kg thrice weekly (U/L)** Range	**Clearance (L/day)** Mean (95% CI)	**Central Volume of Distribution (L)** Mean (95% CI)	**Peripheral Volume of Distribution (L)** Mean (95% CI)
2.28 ± 0.58	1720 to 2600	15.8 (13.2, 18.9)	5.66 (2.76, 11.6)	44.8 (33.2, 60.5)

$C_{avg, ss}$: Average steady-state concentration
CI: Confidence Interval
SD: Standard Deviation

Sialic acid content of the formulation was identified as a factor affecting clearance of asfotase alfa, and body weight was identified as a factor affecting clearance and volume of distribution at steady state. Immunogenicity does not substantially impact asfotase alfa pharmacokinetic exposure. Other covariates such as age, sex and renal function (calculated as eGFR) were not

found to impact pharmacokinetics of asfotase alfa. Based on the expected exposure at the recommended dose, clinically relevant serum asfotase alfa concentrations were maintained across the range of sialic acid contents of the formulation and patient body weights.

Absorption:
Following weekly SC administrations of Strensiq the observed median T_{max} ranged from 1 to 2 days and the absolute bioavailability ranged from 45.8-98.4 %. The mean ± SD observed C_{max} and AUC_{last} were 1020 ± 326 U/L and 284926 ± 79652 U*h/L, respectively for the 2 mg/kg dose group.

Distribution:
Based on the population pharmacokinetic analysis, the estimated central and peripheral volumes of distribution, mean (95% CI), were 5.66 (2.76, 11.6)L and 44.8 (33.2, 60.5)L, respectively. These results indicated that Strensiq was initially distributed primarily in the intra-vascular space and then distributed to the extra-vascular space reflecting its ability to partition into tissues likely including skeletal tissue.

Metabolism:
In vitro or *in vivo* metabolism studies are not considered relevant for recombinant fusion proteins such as Strensiq since the expected metabolism pathway is the normal catabolic degradation of the drug molecule into small peptides and individual amino acid.

Excretion:
Based on the population pharmacokinetic analysis, the estimated mean clearance (95% CI) was 15.8 (13.2, 18.9) L/day. The average (± SD) elimination half-life of Strensiq was 2.28 (± 0.58) days with a range of 0.740 to 9.94 days.

STORAGE AND STABILITY
Strensiq vials must be stored in the original carton until the time of use under refrigerated conditions at 2-8°C and protected from light.

Out of refrigeration, the medicinal product should be kept at room temperature and administered within 1 hour.

DO NOT FREEZE OR SHAKE.
Strensiq is stable for 24 months.

Do not use beyond the expiration date stamped on the carton.

SPECIAL HANDLING INSTRUCTIONS
Each vial of Strensiq is intended for single use only and should only be punctured once. Discard any unused product.

Use aseptic technique.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Strensiq is supplied as a sterile, nonpyrogenic, clear, colourless to slightly yellow aqueous solution for subcutaneous administration.

Composition:

Strensiq is formulated at pH 7.4 and contains:

Asfotase alfa
Sodium chloride
Dibasic sodium phosphate, heptahydrate
Monobasic sodium phosphate, monohydrate
Water for injections

Strensiq does not contain any preservatives.

Packaging:

Strensiq is supplied in a Type I glass vial with a butyl rubber stopper and an aluminum seal with a polypropylene flip-off cap.

Pack size	Filled Volume (Total Volume) mL	Concentration mg/mL	Strength* mg/Vial
12 vials per carton	0.3 (0.43)	40	12
	0.45 (0.58)	40	18
	0.7 (0.83)	40	28
	1.0 (1.13)	40	40
	0.8 (0.93)	100	80

Not all strengths may be marketed.

PART II: SCIENTIFIC INFORMATION

STRENSIQ® (asfotase alfa),indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for STRENSIQ® please refer to Health Canada's Notice of Compliance with conditions - drug products web site:
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.

PHARMACEUTICAL INFORMATION

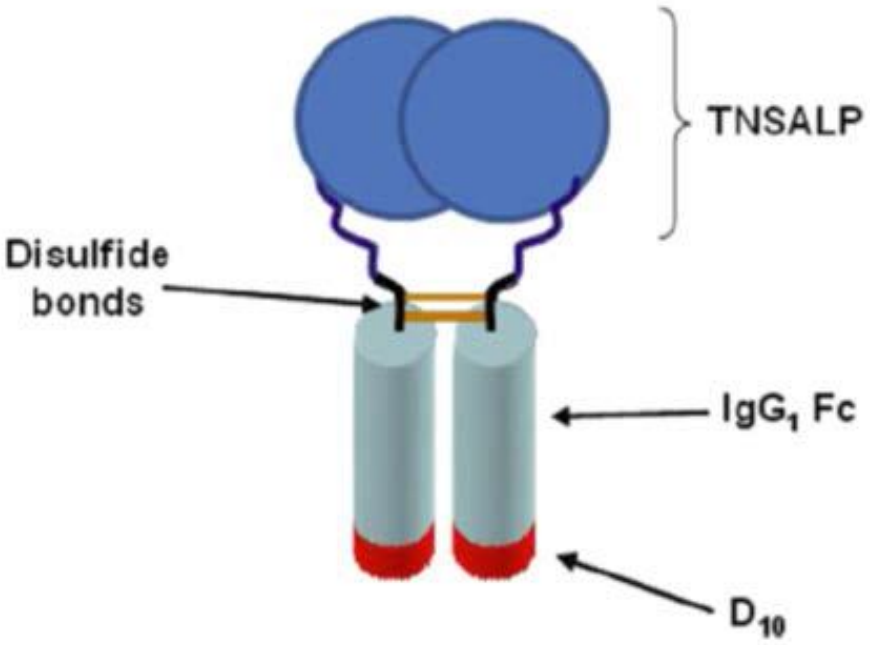
Drug Substance

Proper name: asfotase alfa

Molecular formula and molecular mass: C_{7108} $H_{11,008}$ N_{1968} O_{2206} S_{56};
Theoretical Molecular weight: 161 kDa

Structural formula: Presented in Figure 1.

Figure 1: Representation of the Asfotase Alfa Structure



Product Characteristics
Strensiq (asfotase alfa) is a soluble glycoprotein of 726 amino acids made from the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), the human immunoglobulin G_1 Fc domain and a deca-aspartate peptide used as a bone targeting domain[1,2]. Strensiq is intended for subcutaneous administration. It is supplied as a sterile, nonpyrogenic, clear, colourless, aqueous solution containing 40 mg/mL or 100 mg/mL asfotase alfa, 25 mM sodium phosphate, and 150 mM sodium chloride at a pH between 7.2 and 7.6, inclusive, supplied in a single-use glass vial intended for subcutaneous administration. Strensiq does not contain any preservatives.

Viral Clearance Studies
Three small scale viral clearance studies were performed to assess the capability of the purification process to remove or inactivate Xenotropic Murine Leukaemia Retrovirus (MLV), Pseudorabies Virus (PRV), Reovirus 3 (REO) and Mouse Minute Virus (MMV). The four viruses were chosen to encompass a broad range of physiochemical properties and range of resistance to inactivation and are commercially available at high titers and have well established detection methods. The manufacturing process demonstrates to have adequate viral clearance capacity in viral clearance studies.

NOC/c CLINICAL TRIALS

Data from 52 patients with paediatric HPP onset (including perinatal/infantile (<6 months at onset of symptoms) and juvenile (6 months to 18 years at onset of symptoms) enrolled in 2 pivotal prospective studies and their extensions (ENB-010-10 and ENB-006-09/ENB-008-10) as well as supportive clinical trials (ENB-002-08/ENB-003-08) were used to evaluate the efficacy of Strensiq in the treatment of HPP patients with paediatric onset. A retrospective natural history study ENB-011-10 was conducted to gain additional information on the etiology, range of manifestations, and clinical progression of HPP in patients with perinatal/infantile-onset HPP. In addition, a supportive study (ENB-009-10) enrolled 19 patients aged 13-66 years.

Baseline characteristics of patients with paediatric-onset HPP evaluated in the clinical trials including low ALP and one or more of the following elevated TNSALP biochemical substrates (PPi and PLP), abnormal bone structure (elevated osteoid indices, reduced bone mineral content, skeletal deformities of rickets such as bowed legs, abnormally shaped chest, below normal Z score for height), impaired physical function (gross motor weakness, developmental delay, impaired walking, inability to perform activities of daily living). At baseline patients less than 5 years of age presented with additional morbidities including nephrocalcinosis, seizures, and respiratory compromise (including respiratory failure requiring support) and gross motor delays. In Study ENB-002-08 most patients (9/11, 81.8%) presented with significant gross motor delays on the BSID-III (e.g., Gross Motor scaled scores of 1, which is 3 SDs below the mean [SD] for healthy age-matched peers).

Patient demographics in clinical trials for hypophosphatasia are summarized in Table 3.

Table 3: Summary of Patient Demographics in Clinical Trials of Strensiq for Hypophosphatasia

Study #	Trial design	Dosage, route of administration and duration[a]	Study subjects (n = number)	Mean age (Range)	Gender
ENB-002-08	Multicenter, multinational, open-label, single group assignment, safety/efficacy [Phase 2 in infants and young children (infantile onset)]	Single IV infusion of 2 mg/kg followed by SC injections of 1 mg/kg 3 times per week for 23 weeks	11 enrolled, 10 completed	13.3 mo. (range, 0.6-36 mo)	4 M 7 F
ENB-003-08 (Extension of ENB-002-08)	Multicenter, multinational, open-label, single group assignment, safety/efficacy	SC injections 3 times per week at final dose received in ENB-002-08	10 enrolled, 9 receiving treatment	18 mo. (range, 6-41 mo.)	4 M 6 F
ENB-010-10	Open-label, multicenter, multinational, safety/efficacy, PK [Phase 2 in infants and children (infantile onset)]	SC injections of 2 mg/kg 3 times weekly or 1 mg/kg 6 times weekly (a total of 6 mg/kg/week)	28 enrolled and receiving treatment	27.2 mo. (range, 0-71 mo.)	12 M 16 F
ENB-006-09	Multicenter, multinational, open-label, dose comparison, parallel assignment, historical control, safety/ efficacy, PK, PD [Phase 2 in children and early adolescents (infantile and juvenile onset)]	SC injections of 2 mg/kg or 3 mg/kg 3 times per week (a total of 6 mg/kg/week or 9 mg/kg/week)	13 enrolled (6 in 2 mg/kg group, 7 in 3 mg/kg group), 12 completed (6 in 2 mg/kg group, 6 in 3 mg/kg group	105.5 mo. (range, 71-149 mo.)	11 M 2 F
ENB-008-10 (Extension of ENB-006-09)	Multicenter, multinational, open-label, dose comparison, parallel assignment, safety/ efficacy, PK, PD	1 mg/kg 6 times per week or 2 mg/kg 3 times per week SC injections (a total of 6 mg/kg/week)	12 enrolled and receiving treatment	111 mo. (range, 78-156 mo.)	10 M 2 F

Study #	Trial design	Dosage, route of administration and duration[a]	Study subjects (n = number)	Mean age (Range)	Gender
ENB-009-10	Randomized, open-label, multicenter, multinational, dose-ranging, concurrent control, safety/ efficacy, PK [Phase 2 in adolescents and adults (infantile, juvenile and adult onset)]	Primary treatment period (first 24 weeks of the study): randomization to 1 of the following 3 treatment cohorts: 1. daily SC injections of 0.3 mg/kg (a total of 2.1 mg/kg/week); 2. daily SC injections of 0.5 mg/kg (a total of 3.5 mg/kg/week); or 3. no treatment. Extension period: all patients received daily SC injections of 0.5 mg/kg (a total of 3.5 mg/kg/week) with later transition to 1 mg/kg 6 times per week	19 enrolled (6 in control group, 6 in 0.5 mg/kg group, 7 in 0.3 mg/kg group); 18 receiving treatment in open label extension	491.4 mo. (range, 156-792 mo.)	7 M 12 F

Abbreviations: M = male; F = female; mo. = month; PD = pharmacodynamics; PK = pharmacokinetics; SC=subcutaneous

[a]For all clinical studies except ENB-009-10, dose adjustments were allowed for lack of efficacy or safety-related concerns

Study results

Study ENB-006-09/ENB-008-10

Study ENB-006-09/ENB-008-10 is an ongoing open-label, non-randomised study. 13 patients were enrolled. 5 patients presented with hypophosphatasia before 6 months of age and 8 patients presented after 6 months of age. Age at inclusion in the study ranged from 6 and 12 years old. Among the patients enrolled, 12 patients continue to be a part of this study. The study employed historical controls from the same centre as patients who received asfotase alfa and who had been subject to a similar protocol of clinical management.

<u>Improvement in skeletal system</u> (mineralization, structure, and growth)

<u>Radiographic evidence of healing of HPP-induced rickets</u>

In Study ENB-006-09/ENB-008-10, trained radiologists evaluated pre- and post-baseline x-rays of wrists and knees of patients for the following signs: apparent physeal widening, metaphyseal flaring, irregularity of provisional zone of calcification, metaphyseal radiolucencies, metadiaphyseal sclerosis, osteopenia, 'popcorn' calcification in metadiaphysis, demineralization of distal metaphysis, transverse subphyseal band of lucency and tongues of radiolucency. X-ray

changes from baseline were then rated using the Radiographic Global Impression of Change rating scale as follows: -3=severe worsening, -2=moderate worsening, -1=minimal worsening, 0=no change, +1=minimal healing, +2=substantial healing, +3= near-complete or complete healing. Patients who received asfotase alfa moved to scores of +2 and +3 over the first 6 months of exposure and this was sustained with on-going treatment. Historical controls did not show change over time.

Improvement in bone histomorphology

Bone biopsy:
Tetracycline for bone-labelling was administered in two 3-day courses (separated by a 14-day interval) prior to acquisition of the bone biopsy. Trans-iliac crest bone biopsies were obtained by standard procedure. Histological analysis of biopsies used Osteomeasure software (Osteometrics, USA). Nomenclature, symbols and units followed recommendations of the American Society for Bone and Mineral Research.

For 10 patients in the per-protocol set (excludes those patients who received oral vitamin D between baseline and week 24) who underwent biopsy of the trans-iliac bone crest before and after receiving asfotase alfa:

- Mean (SD) osteoid thickness was 12.8 (3.5) µm at baseline and 9.5 (5.1) µm at week 24
- Mean (SD) osteoid volume / bone volume was 11.8 (5.9)% at baseline and 8.6 (7.2)% at week 24

Improvement in growth
Height, weight and head circumference were plotted on growth charts (series of percentile curves that illustrate distribution) available from the Centers for Disease Control and Prevention, USA. These reference data were drawn from a representative sample of healthy children and are not specific for children with special health care needs: they have been used in the absence of growth charts for children with hypophosphatasia.

In the asfotase alfa treatment group, 9/13 patients displayed persistent apparent catch-up height-gain compared to 1/16 in the historical control group as shown by movement over time to a higher percentile on CDC growth charts. Progress through Tanner stages appeared appropriate.

Some patients required oral vitamin D supplements during the study.

Improvement in physical function and mobility

Strensiq demonstrated improvement in mobility in patients with paediatric onset aged 5 -12 years (ENB-006-09/ENB-008-10) resulting in improvements from Baseline for the 6MWT distance and 6MWT % predicted values. Results were generally observed from Weeks 12 and continued through 192. The observed improvement with asfotase alfa treatment was 125 meters at week 24 and 189 meters at week 120.

Study ENB-010-10
Study ENB-010-10 is an ongoing, open-label, multicenter, multinational, safety/efficacy, Pharmacokinetic (PK) study. 28 patients were enrolled and are receiving treatment in the study. Onset of hypophosphatasia was under 6 months in all patients. Age at inclusion was 0 to 71 months.

The primary efficacy endpoint for this study was the change in rickets severity on skeletal radiographs as measured by the RGI-C scale from Baseline to Week 24. Improvements in rickets severity were reported for patients treated in this study.

At Week 24, the 21/28 (75%) achieved RGI-C scores of 1 or greater, indicative of at least "minimal healing of rickets", 13/28 patients (46.4%) had RGI-C scores of 2 or greater, indicative of "substantial healing of rickets", and 4/28 patients (14.3% of the FA set) achieved scores of 3, indicating "complete or near complete healing of rickets.

Twelve patients were receiving respiratory support at Baseline: 10 patients required ventilation support (via intubation, tracheostomy, BiPAP or CPAP) and 2 patients required only supplemental oxygen.

Of the 16 patients who were not on respiratory support at Baseline, 4 patients required respiratory support (BiPAP or CPAP) during the study. Two of these four patients were weaned from all respiratory support and 2 patients died.

Of the 10 patients who started the study on ventilation support, 4 patients were successfully weaned from all respiratory support after a mean (range) of 48 (24 to 96) weeks of treatment, 1 patient was weaned from invasive mechanical ventilation after 24 weeks of treatment and remains on supplemental oxygen, 1 patient was weaned from invasive mechanical ventilation after 48 weeks of treatment and remains on CPAP, 2 patients remain on invasive mechanical ventilation, and 2 patients died.

Study ENB-002-08/ENB-003-08
Study ENB-002-08/ENB-003-08 is an ongoing, open-label, non-randomised non-controlled study. 11 patients were enrolled and 9 patients are on-going in the study. Onset of hypophosphatasia was under 6 months in all patients. Age at inclusion in the study was between 0.5 to 35 months.

The natural history of untreated infant hypophosphatasia patients suggests high mortality if ventilation is required.

Study ENB-002-08/ENB-03-08 met its primary efficacy endpoint of improvement in rickets severity on skeletal radiographs as measured by the RGI-C at Week 24.

Study ENB-009-10
Study ENB-009-10 is an ongoing, open-label, non-randomised study. 19 patients were enrolled and 18 patients continue to take part in this study. Onset of hypophosphatasia was under 6 months in 4 patients, between 6 months and 18 years in 12 patients and over 18 years in 2 patients. The median duration of Strensiq therapy was approximately 174 weeks (min, max:

96.0, 192.0). Age of onset was not known for 1 patient. Age at inclusion was from 13 to 66 years.

The number of patients 13-18 years of age was limited; therefore results in this age group should be interpreted with caution.

A decrease in PPi levels towards the normal reference range was observed.

DETAILED PHARMACOLOGY

See section **ACTION AND CLINICAL PHARMACOLOGY**.

TOXICOLOGY

Preclinical safety data

In nonclinical safety testing in rats, no body system-specific adverse effects were noted at any dose.

With intravenous use, dose- and time-dependent acute injection reactions that were transient and self-limiting were noted in rats at doses of 1 to 180 mg/kg.

With subcutaneous use, ectopic calcifications and injection site reactions, that were partially to completely reversible, were observed in monkey when asfotase alfa was administered daily at doses up to 10 mg/kg during 26 weeks.

Preclinical data reveal no predicted special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or toxicity to reproduction and development.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of asfotase alfa.

The general toxicology program for asfotase alfa included non-GLP maximum tolerated dose (MTD) studies, definitive toxicity (GLP) studies of varying durations, and a GLP study to compare the local irritation potential of asfotase alfa. One of the MTD studies was a single dose toxicity study in monkeys, and the other was a repeat dose toxicity study in rats. Four-week definitive toxicity studies were then conducted in rats and monkeys using the IV route of administration. Subsequently, chronic six-month monkey (SC) and rat (IV) studies were performed. Reproductive and developmental studies were done in rats and rabbits to determine potential effects on fertility, as well as embryofetal and prenatal/perinatal observations. Stand-alone pharmacology safety studies were conducted to assess the potential effects of asfotase alfa on central nervous system (CNS) and respiratory function in rats. A cardiovascular (CV) pharmacology safety study was conducted as part of the 6-month repeated dose primate toxicity. In general, asfotase alfa was well-tolerated. The only consistent observation was a transient injection reaction observed in rats in most studies following IV injection. Acute reactions were not completely alleviated by antihistamines or a steroid. There was no evidence of complement

involvement in the development of the injection reaction. None of the clinical signs that were typical of the post-dose reaction in rat IV toxicity studies were observed in monkeys or rabbits regardless of the route of administration, or in rats given SC injections. Thus, it is unlikely that these findings are clinically relevant. An immune response to asfotase alfa was evident in several toxicology studies in rats and monkeys. No ADA-related adverse observations were noted either in the general or reproductive toxicology studies. Moreover, the presence of ADA in the toxicology studies was considered irrelevant because asfotase alfa is derived from human proteins. No other observations were made in any of the toxicology studies that would preclude the clinical use of asfotase alfa.

Given that Strensiq is derived from human proteins, and based on its therapeutic indication in a small patient population with significant mortality, studies to assess the effects of Strensiq on the mutagenic and carcinogenic potential were not performed.

REFERENCES

1. Kasugai S, Fujisawa R, et al. Selective drug delivery system to bone: small peptide (Asp) 6 conjugation. *J Bone Miner Res*. 2000; 15(5): 936-43.

2. Nishioka T, Tomatsu S, et al. Enhancement of drug delivery to bone: characterization of human tissue-nonspecific alkaline phosphatase tagged with an acidic oligopeptide. *Mol Genet Metab*. 2006; 88(3): 244-55.

PART III: CONSUMER INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

STRENSIQ® (asfotase alfa) is used as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia.

It has been approved *with conditions*. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

PrSTRENSIQ®

Asfotase alfa Solution for Injection 40 mg/mL & 100 mg/mL

Read this carefully before you start taking **Strensiq**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Strensiq.**

What is Strensiq used for?
Strensiq (asfotase alfa) is indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia (HPP).

Treatment with Strensiq (asfotase alfa) should be initiated by a physician with experience in the management of patients with metabolic bone disorders.

How does Strensiq work?
Strensiq replaces the defective enzyme and prevents or reverses the mineralization defects of the skeleton.

What are the ingredients in Strensiq?
Medicinal ingredients: Asfotase alfa
Non-medicinal ingredients: Sodium chloride; Dibasic sodium phosphate, heptahydrate; Monobasic sodium phosphate, monohydrate; Water for injections.

Strensiq comes in the following dosage forms:
Strensiq is a solution for subcutaneous injection.

Strensiq is supplied in a Type I glass vial with a butyl rubber stopper and an aluminum seal with a polypropylene flip-off cap.

Pack sizes*	Filled Volume (Total Volume) mL	Concentration mg/mL	Strength mg/Vial
12 vials per carton	0.3 (0.43)	40	12
	0.45 (0.58)	40	18
	0.7 (0.83)	40	28
	1.0 (1.13)	40	40
	0.8 (0.93)	100	80

Not all strengths may be marketed.

Do not use Strensiq if:
If you are allergic to asfotase alfa or any of the other ingredients of this medicine (listed under the ingredients).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Strensiq. Talk about any health conditions or problems you may have, including if:

- you are pregnant or think that you may be pregnant;
- you are nursing;
- you have a history of allergic to any ingredient in the formulation;
- you have a kidney disease;
- you have liver disease

Hypersensitivity
Talk to your doctor, pharmacist or nurse if you are experiencing hypersensitive reactions from Strensiq treatment.

Allergic reactions
Patients receiving asfotase alfa have had allergic reactions including life threatening allergic reactions requiring medical treatment called anaphylaxis. Patients who experienced anaphalaxis had symptoms like difficulty breathing, choking sensation, nausea, swelling around the eyes, and dizziness. The reactions occurred within minutes after taking asfotase alfa, and can occur in patients who were taking asfotase alfa for more than one year. If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately.

Children and adolescents
There are no special Strensiq related precautions needed for the treatment of children and adolescents.

Other medicines and Strensiq
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines (prescription or non-prescription medicines).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
The effects on the ability to drive and to use machines have not been studied.

Strensiq contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

Other warnings you should know about:
Talk to your doctor, pharmacist or nurse before using Strensiq.

If you are treated with Strensiq, you may experience a reaction at the injection site during the injection of the medicine or during the hours following the injection.

When injecting regularly, the position on the body where the injections are given should be rotated to a different site with each injection, as this may help reduce pain and irritation. Areas with a substantial amount of fat below the skin are the most suitable areas to inject. Please discuss with you healthcare professional the best sites for you. Please refer to section **How to inject Strensiq**.

Regular injections of Strensiq may lead to a reaction called lipodystrophy. You may experience either an enlargement or thickening of tissue or a depression in the skin at the injection site. Rotating the injection site may reduce the risk of developing this reaction.

Some known eye-related side-effects have been reported in clinical trials with Strensiq, probably associated with hypophosphatasia, talk to your doctor in case of vision trouble.

Patients with HPP are at risk of developing calcium deposits in tissues other than bone, such as the eye and kidney. Your doctor may check for calcium deposits at these sites periodically before and during Strensiq treatment.

Early fusion of the bones of the head in children below 5 years of age has been reported in clinical studies of infants with Hypophosphatasia, with and without use of Strensiq. Talk to your doctor if you notice any change in the shape of your infant's head.

Patients may display disproportionate weight increase. Dietary supervision is recommended.

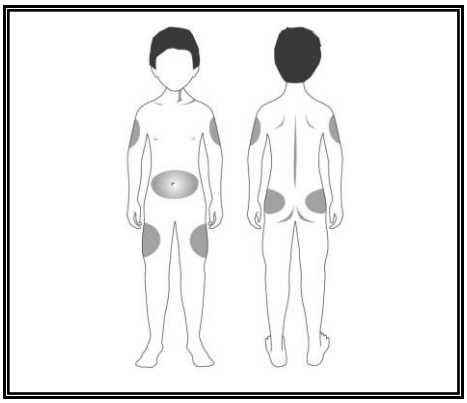
The development of blood proteins against Strensiq, also called anti-drug antibodies, may occur during the treatment. Talk to your doctor if you feel that Strensiq is no longer working as well for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

If you need to undergo laboratory tests (giving blood for testing), tell your doctor that you are treated with Strensiq. Strensiq may cause some tests to show wrongly higher or lower results. Therefore another type of test may need to be used if you are treated with Strensiq.

How to take Strensiq:
If you are injecting this medicine yourself, you will be shown how to prepare and give the injection by your doctor, pharmacist or nurse. Do not inject this medicine yourself unless you have received training and you understand the procedure.

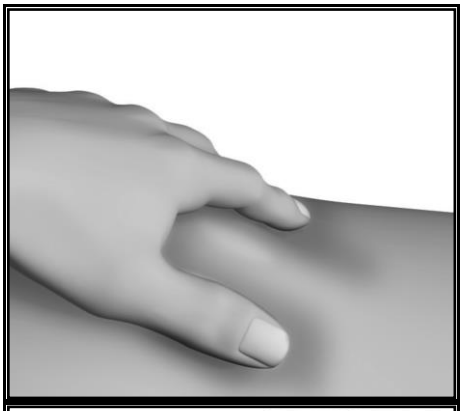
How to inject Strensiq:
Wash your hands thoroughly with soap and water.
Remove the protective cap from the Strensiq vial.
Withdraw the correct dose of Strensiq into the syringe.



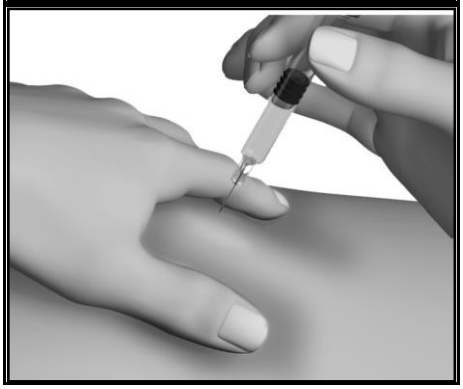
It is important to rotate Strensiq injection sites to reduce the risk of some reactions including lipohypertrophy (enlargement or thickening of tissue) and injection site atrophy (depression in the skin). Do not administer injections in areas that are reddened, inflamed or swollen.

Determine the injection site then, using a 60-70% alcohol-based solution (isopropyl alcohol or ethanol) on a single use or cotton-wool ball, clean the site.

NOTE: Do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor about anything you find.



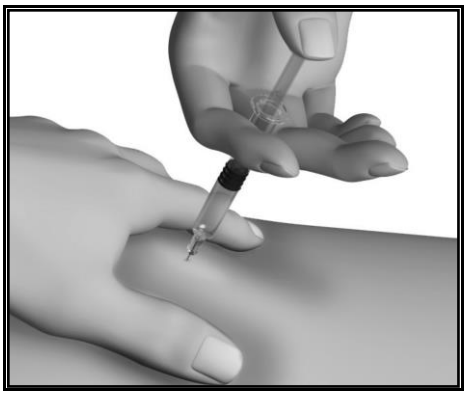
Gently pinch the skin of the chosen injection area between your thumb and index finger.



Subcutaneously administer the prescribed dose to the injection site.

Holding the syringe like a pencil or a dart, insert the needle into the raised skin so it is at an angle of between 45º and 90º to the skin surface.

For patients who have little subcutaneous fat or thin skin, a 45º angle may be preferable.



While continuing to hold the skin, push the syringe plunger to inject the medication while counting slowly to 10.
Remove the needle, release the skin fold and gently place a piece of cotton wool or gauze over the injection site for a few seconds.
This will help seal the punctured tissue and prevent any leakage.
Do not rub the injection site after injection.
Place bandage onto the injection site and properly dispose of the needle.

If you use more Strensiq than you should
If you suspect that you have been accidently administered a higher dose of Strensiq than prescribed, please contact your doctor for advice.

If you forget to use Strensiq
Do not take a double dose to make up for a forgotten dose and please contact your doctor for advice.

Usual dose:
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.

Overdose:
The consequences of an overdose are not known with Strensiq.

If you think you have taken too much Strensiq contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose or Stopping Treatment:
In case of a missed dose, resume the regular schedule as soon as possible. Scheduling of subsequent doses should be determined by the treating physician and the Strensiq dosing regimen. Inform your doctor if you missed a dose. A missed dose should be administered as soon as possible to ensure adequate serum levels of Strensiq.

Strensiq is recommended for the long-term treatment of HPP and stopping treatment may lead to the return of your symptoms including high calcium levels in the blood. Do not stop treatment unless you and your doctor decide there is a significant risk to you to continue receiving Strensiq.

What are possible side effects from using Strensiq?
These are not all the possible side effects you may feel when taking Strensiq. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Injection site reactions (ISRs)	√		
COMMON			
Chills Fever Irritability	√		
Lump under the skin Skin discolouration redness of the skin or mucous membranes	√		
Nausea	√		
Muscle pain	√		
Bruise & increased tendency to bruise		√	
Hot flush	√		
Injection site cellulitis	√		
Headache	√		
Hypersensitivity		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Strensiq vials must be stored in the original carton until the time of use under refrigerated conditions at 2-8°C and protected from light.

Out of refrigeration, the medicinal product should be kept at room temperature and administered within 1 hour.

DO NOT FREEZE OR SHAKE.

Do not use beyond the expiration date stamped on the carton.

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://alxn.com/ or by calling 1-844-MAP-PAM2 (1-844-627-7262).
- Alexion Pharma GmbH has established a Registry for HPP in order to continue to monitor and evaluate the safety and effectiveness of Strensiq®. You are encouraged to participate and advised that participation may involve long-term follow-up. For information regarding the HPP Registry please call 1-844-MAP-PAM2 (1-844-627-7262).You can only participate in the Registry through your doctor.

This leaflet was prepared by Alexion Pharma GmbH.

Date of Approval: May 22, 2019