1. NAME OF THE MEDICINAL PRODUCT

Strensiq® 40 mg/ml, solution for injection
Strensiq® 100 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Strensiq 40 mg/ml solution for injection
Each ml of solution contains 40 mg of asfotase alfa*.

Each vial contains 0.3 ml solution and 12 mg of asfotase alfa (40 mg/ml).
Each vial contains 0.45 ml solution and 18 mg of asfotase alfa (40 mg/ml).
Each vial contains 0.7 ml solution and 28 mg of asfotase alfa (40 mg/ml).
Each vial contains 1.0 ml solution and 40 mg of asfotase alfa (40 mg/ml).

Strensiq 100 mg/ml solution for injection
Each ml of solution contains 100 mg of asfotase alfa*.

Each vial contains 0.8 ml solution and 80 mg of asfotase alfa (100 mg/ml).

* produced by recombinant DNA technology using mammalian Chinese Hamster Ovary (CHO) cell culture.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, slightly opalescent or opalescent, colourless to slightly yellow, aqueous solution; pH 7.4. A few small translucent or white particles may be present.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease (see section 5.1).

4.2 Posology and method of administration

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

Educational materials, "Parents guide for Injection" and "Self injection guide" are available for Strensiq in the Ministry of Health web site at the following links:

- **"Parents guide for Injection" - https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/Strensiq_Parents_guide_for_injection_Final_12_2017.pdf**
- **"Self injection guide" – https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/Strensiq_Self_injection_guide_Final_12_2017.pdf**

Posology
Recommended dosage regimen of asfotase alfa 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 subcutaneously six times per week.

Refer to the dosing chart below for more details.

Body Weight (kg)	If injecting 3x per week			If injecting 6 x per week		
	Dose to be injected	Volume to be injected	Vial type used for injection	Dose to be injected	Volume to be injected	Vial type used for injection
3	6 mg	0.15 ml	0.3 ml			
4	8 mg	0.20 ml	0.3 ml			
5	10 mg	0.25 ml	0.3 ml			
6	12 mg	0.30 ml	0.3 ml	6 mg	0.15 ml	0.3 ml (**STRENSIQ ® 40 MG/ML**)
7	14 mg	0.35 ml	0.45 ml	7 mg	0.18 ml	0.3 ml (**STRENSIQ ® 40 MG/ML**)
8	16 mg	0.40 ml	0.45 ml	8 mg	0.20 ml	0.3 ml (**STRENSIQ ® 40 MG/ML**)
9	18 mg	0.45 ml	0.45 ml	9 mg	0.23 ml	0.3 ml (**STRENSIQ ® 40 MG/ML**)
10	20 mg	0.50 ml	0.7 ml	10 mg	0.25 ml	0.3 ml (**STRENSIQ ® 40 MG/ML**)
11	22 mg	0.55 ml	0.7 ml	11 mg	0.28 ml	0.3 ml (**STRENSIQ ® 40 MG/ML**)
12	24 mg	0.60 ml	0.7 ml	12 mg	0.30 ml	0.3 ml (**STRENSIQ ® 40 MG/ML**)
13	26 mg	0.65 ml	0.7 ml	13 mg	0.33 ml	0.45 ml (**STRENSIQ ® 40 MG/ML**)
14	28 mg	0.70 ml	0.7 ml	14 mg	0.35 ml	0.45 ml (**STRENSIQ ® 40 MG/ML**)
15	30 mg	0.75 ml	1 ml	15 mg	0.38 ml	0.45 ml (**STRENSIQ ® 40 MG/ML**)
16	32 mg	0.80 ml	1 ml	16 mg	0.40 ml	0.45 ml (**STRENSIQ ® 40 MG/ML**)
17	34 mg	0.85 ml	1 ml	17 mg	0.43 ml	0.45 ml (**STRENSIQ ® 40 MG/ML**)
18	36 mg	0.90 ml	1 ml	18 mg	0.45 ml	0.45 ml (**STRENSIQ ® 40 MG/ML**)
19	38 mg	0.95 ml	1 ml	19 mg	0.48 ml	0.7 ml (**STRENSIQ ® 40 MG/ML**)
20	40 mg	1.00 ml	1 ml	20 mg	0.50 ml	0.7 ml (**STRENSIQ ® 40 MG/ML**)
25	50 mg	0.50 ml	0.8 ml	25 mg	0.63 ml	0.7 ml (**STRENSIQ ® 40 MG/ML**)
30	60 mg	0.60 ml	0.8 ml	30 mg	0.75 ml	1 ml (**STRENSIQ ® 40 MG/ML**)
35	70 mg	0.70 ml	0.8 ml	35 mg	0.88 ml	1 ml (**STRENSIQ ® 40 MG/ML**)
40	80 mg	0.80 ml	0.8 ml	40 mg	1.00 ml	1 ml (**STRENSIQ ® 40 MG/ML**)
50				50 mg	0.50 ml	0.8 ml (**STRENSIQ ® 100 MG/ML**)
60				60 mg	0.60 ml	0.8 ml (**STRENSIQ ® 100 MG/ML**)
70				70 mg	0.70 ml	0.8 ml (**STRENSIQ ® 100 MG/ML**)
80				80 mg	0.80 ml	0.8 ml (**STRENSIQ ® 100 MG/ML**)
90				90 mg	0.90 ml	0.8 ml (x2) (**STRENSIQ ® 100 MG/ML**)
100				100 mg	1.00 ml	0.8 ml (x2) (**STRENSIQ ® 100 MG/ML**)

Missed dose
If a dose of asfotase alfa is missed, a double dose should not be injected to make up for the missed dose.

Special population

Adult patients
Efficacy and safety data in patients with hypophosphatasia >18 years old are limited.

Elderly
The safety and efficacy of asfotase alfa in elderly patients have not been established and no specific dose regimen can be recommended for these patients.

Renal impairment
The safety and efficacy of asfotase alfa in patients with renal impairment have not been evaluated and no specific dose regimen can be recommended for these patients.

Hepatic impairment
The safety and efficacy of asfotase alfa in patients with hepatic impairment have not been evaluated and no specific dose regimen can be recommended for these patients.

Method of administration

Strensiq is for subcutaneous use only. It is not intended for intravenous or intramuscular injection.
The maximum volume of medicinal product per injection should not exceed 1 ml. If more than 1 ml is required, multiple injections may be administered at the same time.
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.

Injections sites should be rotated and carefully monitored for signs of potential reactions (see section 4.4).

Patients can self-inject only if they have properly been trained on administration procedures.
For handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Hypersensitivity reactions including signs and symptoms consistent with anaphylaxis have been reported in patients treated with asfotase alfa (see section 4.8). These symptoms included difficulty breathing, choking sensation, periorbital edema, and dizziness. The reactions have occurred within minutes after subcutaneous administration of asfotase alfa and can occur in patients on treatment for more than 1 year. Other hypersensitivity reactions included vomiting, nausea, fever, headache, flushing, irritability, chills, skin erythema, rash, pruritus, and oral hypoaesthesia. If these reactions occur, immediate discontinuation of treatment is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment should be observed.

Consider the risks and benefits of re-administering asfotase alfa to individual patients following a severe reaction, taking other factors into account that may contribute to the risk of a hypersensitivity reaction, such as concurrent infection and/ or use of antibiotics. If the decision is made to re-administer the product, the re-challenge should be made under medical supervision and consideration may be given to use of appropriate pre-medication. Patients should be monitored for recurrence of signs and symptoms of a severe hypersensitivity reaction.

The need for supervision for subsequent administrations and need for emergency treatment for home care should be at the discretion of the treating physician.

Severe or potentially life-threatening hypersensitivity is a contraindication to re-challenge, if hypersensitivity is not controllable (see section 4.3).

Injection reaction

Administration of asfotase alfa may result in local injection site reactions (including, but not limited to, erythema, rash, discoloration, pruritus, pain, papule, nodule, atrophy) defined as any related adverse event occurring during the injection or until the end of the injection day (see section 4.8). Rotation of injection sites may help to minimize these reactions.
Strensiq administration should be interrupted in any patient experiencing severe injection reactions and appropriate medical therapy administered.

Lipodystrophy

Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with asfotase alfa in clinical trials (see section 4.8). Patients are advised to follow proper injection technique and to rotate injection sites (see section 4.2).

Craniosynostosis

In asfotase alfa clinical studies adverse events of craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis and occurrence of Arnold-Chiari malformation, have been reported in hypophosphatasia patients < 5 years of age. There are insufficient data to establish a causal relationship between exposure to Strensiq and progression of 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 hypophosphatasia patients below 5 years of age.

Ectopic calcification

In asfotase alfa clinical studies ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis have been reported in patients with hypophosphatasia. There are insufficient data to establish a causal relationship between exposure to asfotase alfa and ectopic calcification. Ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis as manifestations of hypophosphatasia are documented in published literature. Nephrocalcinosis occurred in 51.6% of patients between birth and 5 years of age in a natural history study of untreated infantile-onset hypophosphatasia patients. Ophthalmology examination and renal ultrasounds are recommended at baseline and periodically in hypophosphatasia patients.

Serum Parathyroid Hormone and Calcium

Serum parathyroid hormone concentration may increase in hypophosphatasia patients administered asfotase alfa, most notably during the first 12 weeks of treatment. It is recommended that serum parathyroid hormone and calcium be monitored in patients treated with asfotase alfa. Supplements of calcium and oral vitamin D may be required. See section 5.1.

Disproportionate weight gain

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

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. the product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with asfotase alfa. Based on its structure and pharmacokinetics, asfotase alfa is unlikely to affect Cytochrome P-450 related metabolism.

Asfotase alfa contains a catalytic domain of tissue non-specific alkaline phosphatase. Administration of asfotase alfa will interfere with routine measurement of serum alkaline phosphatase by hospital laboratories resulting in serum alkaline phosphatase activity measurements of several thousand units per litre. Asfotase alfa activity results must not be interpreted as the same measure as serum alkaline phosphatase activity owing to differences in enzyme characteristics.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data from the use of asfotase alfa in pregnant women.
Following repeated subcutaneous administration to pregnant mice in the therapeutic dose range (>0.5 mg/kg), asfotase alfa levels were quantifiable in fetuses at all doses tested, suggesting cross-placental transport of asfotase alfa. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Asfotase alfa is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
There is insufficient information on the excretion of asfotase alfa in human milk. A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from asfotase alfa therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Preclinical fertility studies were conducted and showed no evidence of effect on fertility and embryo-fetal development (see section 5.3).

4.7 Effects on ability to drive and use machines

Strensiq has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Supportive safety data reflect exposure in 112 patients with perinatal/infantile (n=89), juvenile-onset (n = 22), adult onset (n = 1) HPP (age at enrollment from 1 day to 66.5 years) treated with asfotase alfa, with a treatment duration range from 1 day to 391.9 weeks [7.5 years]). The most common adverse reactions observed were injection site reactions (74%). A few case reports of anaphylactoid/hypersensitivity reaction have been received

Tabulated list of adverse reactions

Adverse reactions with asfotase alfa are listed by system organ class and preferred term using MedDRA frequency convention very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse Reactions Reported in clinical trials in hypophosphatasia patients

System Organ Class	Frequency category	Adverse reaction
Infections and infestations	Common	Injection site cellulitis
Blood and lymphatic system disorders	Common	Increased tendency to bruise
Immune system disorders	Common	Anaphylactoid reactions Hypersensitivity[2]
Metabolism and nutrition disorders	Common	Hypocalcaemia
Nervous system disorders	Very common	Headache
Vascular disorders	Common	Hot flush
Gastrointestinal disorders	Common	Hypoaesthesia oral Nausea
Skin and subcutaneous tissue disorders	Very common	Erythema
	Common	Skin discolouration Skin disorder (stretched skin)
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity
	Common	Myalgia
Renal and urinary disorders	Common	Nephrolithiasis
General disorders and administration site conditions	Very common	Injection site reactions[1] Pyrexia Irritability
	Common	Chills
Injury, poisoning and procedural complications	Very common	Contusion
	Common	Scar

[1]- ***Preferred terms considered as injection site reactions are presented in section below***

[2]- ***Preferred terms considered as hypersensitivity are presented in the section below***

Description of selected adverse reactions

Injection site reactions

Injection site reactions (including injection site atrophy, abscess, erythema, discolouration, pain, pruritus, macule, swelling, contusion, bruising, lipodystrophy (lipoatrophy or lipohypertrophy), induration, reaction, nodule, rash, papule, haematoma, inflammation, urticarial, calcification, warmth, haemorrhage, cellulitis, scar, mass, extravasation, exfoliation and vesicles) are the most common adverse reactions observed in about 74% of the patients in clinical studies. Most injection site reactions were mild and self-limiting, and the majority (> 99%) were reported as non- serious. In the clinical trial setting, the majority of patients who experienced an injection site reaction had the first occurrence within the first 12 weeks of treatment with asfotase alfa, and some patients continued to experience injection site reactions until 1 or more years after initiating asfotase alfa dosing.
One patient withdrew from the trial due to injection site hypersensitivity.

Hypersensitivity
Hypersensitivity reactions include erythema/redness, pyrexia/fever, rash, pruritis, irritability, nausea, vomiting, pain, rigor/chills, hypoaesthesia oral, headache, flushing, tachycardia, cough, and signs and symptoms consistent with anaphylaxis (see section 4.4). A few case reports of anaphylactoid/hypersensitivity reaction have also been received and were associated with signs and symptoms of difficulty breathing, choking sensation, periorbital edema and dizziness.

Immunogenicity
There is potential for immunogenicity. Among 109 hypophosphatasia patients enrolled in the clinical studies and who have post baseline antibody data available, 97/109 (89. 0%) tested positive for anti-drug antibodies at some time point after starting Strensiq treatment. Among those 97 patients, 55 (56.7%) also showed the presence of neutralizing antibodies at some time point post-baseline. The antibody response (with or without presence of neutralizing antibodies) was time variant in nature. In clinical trials, the development of antibodies has not been shown to affect clinical efficacy or safety (see section 5.2). Data from post-marketing cases suggests that the development of antibodies may affect clinical efficacy.

No trends in adverse events based on antibody status were observed in clinical trials. Some patients confirmed positive for antidrug antibodies experienced injection site reactions (ISRs) and/or hypersensitivity, however there was no consistent trend in the frequency of these reactions over time noted between ADA ever positive and ADA always negative patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
And emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

There is limited experience with overdose of asfotase alfa. The maximum dose of asfotase alfa used in clinical studies is 28 mg/kg/week. No dose-related toxicity or change in the safety profile has been observed in clinical studies. Therefore, no overdose level has been determined. For management of adverse reactions, see sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB13

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein that is expressed in an engineered Chinese hamster ovary cell line. Asfotase alfa is a soluble glycoprotein comprised of two identical polypeptide chains, each with a length of 726 amino acids made from (i) the catalytic domain of human tissue-nonspecific alkaline phosphatase, (ii) the human immunoglobulin G1 Fc domain and (iii) a deca-aspartate peptide domain.

Hypophosphatasia
Hypophosphatasia is a rare, severe, and potentially fatal, genetic disorder caused by loss-of-function mutation(s) in the gene encoding tissue non-specific alkaline phosphatase. Hypophosphatasia is associated with multiple bone manifestations including rickets / osteomalacia, altered calcium and phosphate metabolism, impaired growth and mobility, respiratory compromise that may require ventilation, and vitamin B6-responsive seizures.

Mechanism of action

Asfotase alfa, a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein with enzymatic activity, promotes mineralisation of the skeleton in patients with hypophosphatasia.

Clinical efficacy and safety

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

Study ENB-006-09/ENB-008-10 was an open-label, randomised study. Thirteen patients were enrolled, 12 completed, and 1 discontinued (discontinuation early in the study due to a previously planned elective scoliosis surgery). At study completion patients had received a median of over 76 months (6.3 years) of treatment (1 to 79 months). Five patients presented with symptoms of hypophosphatasia before 6 months age and 8 patients presented after 6 months age. Age at inclusion in the study was between 6 and 12 years old and was between 10 and 18 years old at completion, with 9 patients who became between 13 and 17 years old during the study.
The study employed historical controls from the same centres as patients who received asfotase alfa and who had been subject to a similar protocol of clinical management.

The effects of asfotase alfa on x-ray appearance

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. The majority of the 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.

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
- Mean (SD) mineralisation lag-time was 93 (70) days at baseline and 119 (225) days at week 24

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.
For those patients who received asfotase alfa: 11/13 patients displayed persistent apparent catch-up height-gain as shown by movement over time to a higher percentile on CDC growth charts.
1/13 patients did not display apparent catch-up height-gain and 1 patient did not have enough data to permit judgement. Progress through Tanner stages appeared appropriate.
For the time period of observation of historical controls: 1/16 patients displayed apparent catch-up height-gain, 12/16 patients did not display apparent catch-up height-gain and data were inconclusive in 3/16 patients.

Some patients required oral vitamin D supplements during the study (see sections 4.4 and 4.8).

Study ENB-002-08/ENB-003-08
Study ENB-002-08/ENB-003-08 was an open-label, non-randomised, non-controlled study.
11 patients were enrolled in the initial study and 10 patients entered the extension study, with 9 patients completing the extension study. At study completion, patients had received a median of over 79 months (6.6 years) of treatment (1 to >84 months). Onset of hypophosphatasia was under 6 months in all patients. Age at treatment initiation in the study was between 0.5 to 35 months.
7/11 patients in the full analysis set achieved Radiographic Global Impression of Change scores of +2 at Week 24 compared to baseline radiographs. The improvement in rickets severity was maintained for at least 72 months of follow-up treatment (including at least 84 months in 4 patients), as measured by the RGI C.
5/11 subjects displayed apparent catch-up height-gain. At last assessment (n = 10, 9 of whom had at least 72 months of treatment), median Z-score improvements from baseline were 1.93 for length/height and 2.43 for weight. Fluctuation in height-gain was apparent and may reflect the more severe disease and higher rate of morbidity in these younger patients.

Study ENB-010-10
Study ENB-010-10 was a controlled open-label study in 69 patients, aged 1 day to 72 months, with perinatal/infantile-onset HPP. The mean age at sign/symptom onset was 1.49 months. Patients received STRENSIQ at 6 mg/kg per week for the first 4 weeks. All patients began the study on a dose of asfotase alfa 6 mg/kg per week. The dose of asfotase alfa was increased for 11 patients during the study. Of these 11 patients, 9 patients had their doses increased specifically to improve clinical response. Thirty-eight patients were treated for at least 2 years (24 months) and 6 patients have been treated for at least 5 years (60 months).
At Week 48, 50/69 patients (72.5%) in the full analysis set achieved Radiographic Global Impression of Change scores ≥ 2, and were considered responders. Improvements in median RGI-C were maintained over the course of treatment, which ranged from 0.9 to 302.3 weeks, even if fewer patients were followed after Week 96 (a total of 29 patients were followed after Week 96 and ≤ 8 patients after Week 192).
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 (CDC), USA. A total of 24/69 (35%) patients displayed apparent catch-up height-gain and 32/69 (46%) patients displayed apparent catch-up weight-gain, as shown by movement over time to a higher percentile on CDC growth charts. 40/69 patients and 32/69 patients did not show apparent catch-up gain in height and in weight, respectively. 4 patients did not have enough data to permit judgement and 1 patient could not be determined with certainty.

Study ENB-009-10
Study ENB-009-10 was an open-label, randomised study. The patients were randomly assigned to treatment group for the primary treatment period. Nineteen patients were enrolled, 14 completed, and 5 discontinued. At study completion patients had received a median of over 60 months of treatment (24 to 68 months). The onset of hypophosphatasia was under 6 months in 4 patients, between 6 months and 17 years in 14 patients, and over 18 years in one patient. Age at inclusion was from 13 to 66 years and was between 17 and 72 years at study completion.

The adolescent (and adult) patients in this study did not display apparent height-gain.
Patients underwent biopsy of the trans-iliac bone crest either as part of a control group or before and after exposure to asfotase alfa:

- Control group, standard of care (5 evaluable patients): mean (SD) mineralisation lag-time was 226 (248) days at baseline and 304 (211) days at week 24
- 0.3 mg/kg/day asfotase alfa group (4 evaluable patients): mean (SD) mineralisation lag-time was 1236 (1468) days at baseline and 328 (200) days at week 48
- 0.5 mg/kg/day asfotase alfa group (5 evaluable patients): mean (SD) mineralisation lag-time was 257 (146) days at baseline and 130 (142) days at week 48

After approximately 48 weeks all patients were adjusted to the recommended dose 1.0 mg/kg/day.

Ventilation support

In studies ENB-002-08/ENB-003-08 (11 patients) and ENB-010-10 (69 patients), both open-label, non-randomised, non-controlled studies of patients aged 0.1 to 312 weeks at baseline. 69 patients completed the studies, and 11 discontinued. Patients received a median duration of treatment of 27.6 month (range from 1 day to 90 months). 29 of 80 patients required ventilation support at baseline:

· 16 patients required invasive ventilation support (intubation or tracheostomy) at baseline (one had a brief period of non-invasive ventilation at baseline before transfer).
  - 7 patients were weaned off invasive ventilation (time on ventilation from 12 to 168 weeks), 4 patients were off any ventilation support, and 3 patients were on non-invasive ventilation support. Five out of 7 patients achieved an RGI-C score ≥2
  -5 patients continued with invasive ventilation support, 4 of them with RGI-C score <2
  - 3 patients died whilst on ventilation support
  - 1 patient withdrew consent

· 13 patients required non-invasive ventilation support at baseline.
  - 10 patients were weaned off any ventilation support (time on ventilation from 3 to 216 weeks). 9 out of 10 patients achieved a RGI-C score ≥2, only 1 with RGI-C <2.
  - 2 patients required invasive ventilation support and 1 patient continued with non-invasive ventilation support, all 3 patients died and with RGI-C score <2

The natural history of untreated infantile-onset hypophosphatasia patients suggests high mortality if ventilation is required.

Due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product, in case new information become available, this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Pharmacokinetics of asfotase alfa were evaluated in a 1-month, multicenter, open-label, dose-escalating, study in adults with hypophosphatasia. Cohort 1 (n=3) of the study received asfotase alfa 3 mg/kg intravenously the first week followed by 3 doses at 1 mg/kg subcutaneous at weekly intervals from weeks 2 to 4. Cohort 2 (n=3) received asfotase alfa 3 mg/kg intravenously the first week followed by 3 doses at 2 mg/kg subcutaneous at weekly intervals from weeks 2 to 4. After the 3 mg/kg for 1.08 hours intravenous infusion, the median time (T_{max}) ranged between 1.25 to 1.50 hours, and the mean (SD) C_{max} ranged between 42694 (8443) and 46890 (6635) U/L over the studied cohorts. The absolute bioavailability after the first and third subcutaneous administration ranged from 45.8 to 98.4%, with median T_{max} ranging between 24.2 to 48.1 hours. After the 1 mg/kg weekly subcutaneous administration in Cohort 1 the mean (SD) AUC over the dosing interval (AUCτ) was 66034 (19241) and 40444 (N=1) U*h/L following the first and the third dose, respectively. After the 2 mg/kg weekly subcutaneous administration in Cohort 2 the mean (SD) AUCτ was 138595 (6958) and 136109 (41875) following the first and the third dose, respectively.

Pharmacokinetic data from all asfotase alfa clinical trials were analysed using population pharmacokinetic methods. The pharmacokinetic variables characterized by population pharmacokinetic analysis represent the overall hypophosphatasia patient population with age range from 1 day to 66 years, subcutaneous doses of up to 28 mg/kg/week and a range of disease onset cohorts. Twenty five percent (15 out of 60) of the overall patient population was adult (>18 years) at baseline. The absolute bioavailability and absorption rate following subcutaneous administration were estimated to be 0.602 (95% CI: 0.567, 0.638) or 60.2% and 0.572 (95%CI: 0.338, 0.967)/day or 57.2%, respectively. The central and peripheral volumes of distribution estimates for a patient with body weight of 70 kg (and 95% CI) were 5.66 (2.76, 11.6) L and 44.8 (33.2, 60.5) L, respectively. The central and peripheral clearance estimates for a patient with body weight of 70 kg (and 95% CI) were 15.8 (13.2, 18.9) L/day and 51.9 (44.0, 61.2) L/day, respectively. The extrinsic factors affecting asfotase alfa pharmacokinetic exposures were formulation specific activity and total sialic acid

content. The average ± SD elimination half-life following subcutaneous administration was 2.28 ± 0.58 days.
In adult patients with pediatric-onset HPP, the pharmacokinetics of asfotase alfa at doses of 0.5, 2 and 3 mg/kg administered three times per week was consistent with those observed in pediatric patients with pediatric-onset HPP, and thus supported the approved dose of 6 mg/kg per week in treating adult patients with pediatric-onset HPP.

Linearity/non-linearity
Based on the results of population pharmacokinetic analysis it was concluded that asfotase alfa exhibits linear pharmacokinetic up to subcutaneous doses of 28 mg/kg/week. The model identified body weight to affect asfotase alfa clearance and volume of distribution parameters. It is expected that pharmacokinetic exposures will increase with body weight. The impact of immunogenicity on asfotase alfa pharmacokinetic varied over time due to the time varying nature of immunogenicity and overall was estimated to decrease pharmacokinetic exposures by less than 20%.

5.3 Preclinical safety data

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

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

Ectopic calcifications and injection site reactions were observed in monkeys when asfotase alfa was administered subcutaneously at daily doses up to 10 mg/kg through 26 weeks. These effects were restricted to injection sites and were partially or completely reversible.
There was no evidence of ectopic calcification observed in any other tissues examined.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or toxicity to reproduction and development. However, in pregnant rabbits administered intravenous doses of up to 50 mg/kg/day asfotase alfa, anti-drug antibodies were detected in up to 75% of animals which could affect the detection of reproductive toxicity.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Chemical and physical in-use stability has been demonstrated for up to 3 hours at a temperature between 23°C to 27°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass with a stopper (butyl rubber) and a seal (aluminium) with a flip-off cap (polypropylene).

Strensiq 40 mg/ml solution for injection
Filled volumes of the vials are: 0.3 ml, 0.45 ml, 0.7 ml and 1.0 ml

Strensiq 100 mg/ml solution for injection
Filled volumes of the vials are: 0.8 ml

Pack sizes of 1 or 12 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only and should only be punctured once. Any unused solution in the vial should be discarded.

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. An aseptic technique should be used.

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

7. MANUFACTURER

Alexion Pharma International Operations Limited, College Business and Technology Park, Blanchardstown, Dublin 15, Ireland.

8. REGISTRATION HOLDER

Alexion Pharma Israel Ltd, POB 7063, Petach Tikva 4917001.

9. REGISTRATION NUMBERS

Strensiq® 40 mg/ml	155-43-34542
Strensiq® 100 mg/ml	155-44-34545

Revised in July 2023 according to MOHs guidelines