**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 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.

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.
Maximum recommended dose of asfotase alfa is 6 mg/kg/week (see Section 5.1).

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 |
| **7** | 14 mg | 0.35 ml | 0.45 ml | 7 mg | 0.18 ml | 0.3 ml |
| **8** | 16 mg | 0.40 ml | 0.45 ml | 8 mg | 0.20 ml | 0.3 ml |
| **9** | 18 mg | 0.45 ml | 0.45 ml | 9 mg | 0.23 ml | 0.3 ml |
| **10** | 20 mg | 0.50 ml | 0.7 ml | 10 mg | 0.25 ml | 0.3 ml |
| **11** | 22 mg | 0.55 ml | 0.7 ml | 11 mg | 0.28 ml | 0.3 ml |
| **12** | 24 mg | 0.60 ml | 0.7 ml | 12 mg | 0.30 ml | 0.3 ml |
| **13** | 26 mg | 0.65 ml | 0.7 ml | 13 mg | 0.33 ml | 0.45 ml |
| **14** | 28 mg | 0.70 ml | 0.7 ml | 14 mg | 0.35 ml | 0.45 ml |
| **15** | 30 mg | 0.75 ml | 1 ml | 15 mg | 0.38 ml | 0.45 ml |
| **16** | 32 mg | 0.80 ml | 1 ml | 16 mg | 0.40 ml | 0.45 ml |
| **17** | 34 mg | 0.85 ml | 1 ml | 17 mg | 0.43 ml | 0.45 ml |
| **18** | 36 mg | 0.90 ml | 1 ml | 18 mg | 0.45 ml | 0.45 ml |
| **19** | 38 mg | 0.95 ml | 1 ml | 19 mg | 0.48 ml | 0.7 ml |
| **20** | 40 mg | 1.00 ml | 1 ml | 20 mg | 0.50 ml | 0.7 ml |
| **25** | 50 mg | 0.50 ml | 0.8 ml | 25 mg | 0.63 ml | 0.7 ml |
| **30** | 60 mg | 0.60 ml | 0.8 ml | 30 mg | 0.75 ml | 1 ml |
| **35** | 70 mg | 0.70 ml | 0.8 ml | 35 mg | 0.88 ml | 1 ml |
| **40** | 80 mg | 0.80 ml | 0.8 ml | 40 mg | 1.00 ml | 1 ml |
| **50** | | | | 50 mg | 0.50 ml | 0.8 ml |
| **60** | | | | 60 mg | 0.60 ml | 0.8 ml |
| **70** | | | | 70 mg | 0.70 ml | 0.8 ml |
| **80** | | | | 80 mg | 0.80 ml | 0.8 ml |
| **90** | | | | 90 mg | 0.90 ml | 0.8 ml (x2) |
| **100** | | | | 100 mg | 1.00 ml | 0.8 ml (x2) |

*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*
The pharmacokinetics, pharmacodynamics, and safety of asfotase alfa have been studied in patients with hypophosphatasia > 18 years old. Dose adjustment is not needed in adult patients with paediatric-onset hypophosphatasia (HPP) (see Sections 5.1 and 5.2).

*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<br>Hypersensitivity[2] |
| Metabolism and nutrition disorders | Common | Hypocalcaemia |
| Nervous system disorders | Very common | Headache |
| Vascular disorders | Common | Hot flush |
| Gastrointestinal disorders | Common | Hypoaesthesia oral<br>Nausea |
| Skin and subcutaneous tissue disorders | Very common | Erythema |
| | Common | Skin discolouration<br>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]<br>Pyrexia<br>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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 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.

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and 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

30 months

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 vial 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. MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

## 8. MARKETING AUTHORISATION NUMBER(S)

Strensiq 40 mg/ml solution for injection

EU/1/15/1015/001
EU/1/15/1015/002
EU/1/15/1015/005
EU/1/15/1015/006
EU/1/15/1015/007
EU/1/15/1015/008
EU/1/15/1015/009
EU/1/15/1015/010

Strensiq 100 mg/ml solution for injection

EU/1/15/1015/003
EU/1/15/1015/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28/08/2015
Date of latest renewal: 28/04/2020

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Biologics
101 International Drive
Pease International Tradeport
03801 Portsmouth
United States

Name and address of the manufacturer responsible for batch release

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

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Strensiq in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media,

distribution modalities, and any other aspects of the programme, with the National Competent Authority.
The educational programme is aimed to provide instruction to patients and carers for proper administration techniques to address the risks of medication errors and injection site and injection associated reactions, including hypersensitivity.
The MAH shall ensure that in each Member State where Strensiq is marketed all patients/parents or caregivers who are expected to use Strensiq are provided with the following educational package:

- Self-injection guide for patients
- Injection guide for parents or caregivers with infant patients

Educational materials for patients and caregivers shall contain the following key messages:

- Warning and precautions on the potential risk of medication errors and injection site reactions associated with the use of Strensiq
- Hypersensitivity reactions have been observed in patients treated with Strensiq, including a description of sign and symptoms
- Instructions on the correct dose to be administered
- Instruction on how the injection site is chosen and how the injection is carried out and recorded
- Detailed description on how Strensiq is injected using aseptic techniques
- Information on cold chain management for Strensiq during storage and travel
- Information on reporting side effect

## E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| The MAH should set up an observational, longitudinal, prospective, long-term registry of patients with HPP to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq. | Annually within annual reassessment |

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON 40 mg/ml**

## 1. NAME OF THE MEDICINAL PRODUCT

Strensiq 40 mg/ml solution for injection
asfotase alfa

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution contains 40 mg of asfotase alfa.
Each vial contains 12 mg of asfotase alfa (12 mg/0.3 ml).
Each vial contains 18 mg of asfotase alfa (18 mg/0.45 ml).
Each vial contains 28 mg of asfotase alfa (28 mg/0.7 ml).
Each vial contains 40 mg of asfotase alfa (40 mg/1 ml).

## 3. LIST OF EXCIPIENTS

List of excipients: Sodium chloride, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, water for injections.

See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial of 0.3[0.45; 0.7; 1] ml
12 vials of 0.3[0.45; 0.7; 1] ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original pack in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution should be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1015/001
EU/1/15/1015/002
EU/1/15/1015/005
EU/1/15/1015/006
EU/1/15/1015/007
EU/1/15/1015/008
EU/1/15/1015/009
EU/1/15/1015/010

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

STRENSIQ 40 mg/ml
12 mg/0.3 ml
18 mg/0.45 ml
28 mg/0.7 ml
40 mg/1 ml

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL 40 mg/ml**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Strensiq 40 mg/ml injection
Strensiq 40 mg/ml injection
Strensiq 40 mg/ml injection
Strensiq 40 mg/ml injection
asfotase alfa
SC

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

12 mg/0.3 ml
18 mg/0.45 ml
28 mg/0.7 ml
40 mg/1 ml

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON 100 mg/ml**

## 1. NAME OF THE MEDICINAL PRODUCT

Strensiq 100 mg/ml solution for injection
asfotase alfa

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

List of excipients: Sodium chloride, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, water for injections

See package leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 vial of 0.8 mL
12 vials of 0.8 mL

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original pack in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution should be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1015/003
EU/1/15/1015/004

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

STRENSIQ 100 mg/ml
80 mg/0.8 ml

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL 100 mg/ml**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Strensiq 100 mg/ml injection
asfotase alfa
SC

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

80 mg/0.8 ml

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Strensiq 40 mg/ml solution for injection**
**(12 mg/0.3 ml 18 mg/0.45 ml 28 mg/0.7 ml 40 mg/1 ml)**
asfotase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Strensiq is and what it is used for

**What is Strensiq**
Strensiq is a medicine used to treat the inherited disease hypophosphatasia that started in childhood. It contains the active substance asfotase alfa.

**What is hypophosphatasia**
Patients with hypophosphatasia have low levels of an enzyme called alkaline phosphatase that is important for various body functions, including the proper hardening of bones and teeth. Patients have problems with bone growth and strength, which can lead to broken bones, bone pain, and difficulty walking, as well as difficulties with breathing and a risk of seizures (fits).

**What is Strensiq used for**
The active substance in Strensiq can replace the missing enzyme (alkaline phosphatase) in hypophosphatasia. It is used for long-term enzyme replacement treatment to manage symptoms.

**What benefits of Strensiq have been shown in clinical studies**
Strensiq has shown benefits for patients' mineralization of the skeleton and growth.

## 2. What you need to know before you use Strensiq

**Do not use Strensiq**
If you are severely allergic to asfotase alfa (see section 'Warnings and precautions' below) or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor before using Strensiq.

- Patients receiving asfotase alfa have had allergic reactions including life threatening allergic reactions requiring medical treatment similar to anaphylaxis. Patients who experienced anaphylaxis-like symptoms had 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.
  Should you experience anaphylactic reaction, or an event with similar symptoms, your doctor will discuss with you the next steps and the possibility to restart Strensiq under medical supervision. Always follow the instructions provided by your doctor.
- The development of blood proteins against Strensiq, also called anti-drug antibodies, may occur during the treatment. Talk to your doctor if you experience decreased efficacy with Strensiq.
- Fatty lumps or decreased fatty tissue on the surface of the skin (localized lipodystrophy) have been reported at injection sites after several months in patients using Strensiq. Read section 3 carefully to know the injection recommendations. This is important to rotate the injection from among the following sites to reduce the risk of lipodystrophy: abdominal area, thigh, or deltoid.
- In studies, some eye-related side-effects (e.g. calcium build-up on the eye [conjunctival and corneal calcification]) have been reported both in patients using Strensiq and those who were not, probably associated with hypophosphatasia. Talk to your doctor in case of problems with your vision.
- Early fusion of the bones of the head (craniosynostosis) 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.
- If you are treated with Strensiq, you may experience a reaction at the injection site (pain, nodule, rash, discoloration) during the injection of the medicine or during the hours following the injection. If you experience any severe reaction at the injection site, tell your doctor immediately.
- Increase of parathyroid hormone concentration and low calcium levels have been reported in studies. As a consequence, your doctor may ask you to take supplements of calcium and oral vitamin D if needed.
- Weight gain may occur during your treatment with Strensiq. Your doctor will provide dietary advice as necessary.

**Other medicines and Strensiq**
Tell your doctor or pharmacist if you are using, have recently used or might use any other 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.

**Pregnancy**
Strensiq should not be used during pregnancy. The use of effective birth control during treatment should be considered in women who are able to get pregnant.

**Breast-feeding**
It is not known whether Strensiq can pass into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Strensiq, considering the benefit of breast-feeding to the baby and the benefit of Strensiq to the mother.

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**
This medicine is not expected to have any effect on the ability to drive or use machines.

**Important information about some of the ingredients of Strensiq**
This medicine contains less than 1 mmol sodium (23 mg) per vial, which means it is essentially 'sodium-free'.

## 3. How to use Strensiq

Always use this medicine exactly as described in this leaflet or as your doctor, or pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.
How to use Strensiq will be explained to you by a doctor who is experienced in the management of patients with metabolic or bone related diseases. After being trained by the doctor or specialized nurse, you can inject Strensiq yourself at home.

**Dose**
- The dose you receive is based on your body weight.
- The correct dose will be calculated by your doctor and consists of a total of 6 mg of asfotase alfa per kg of body weight every week, given either as an injection of 1 mg/kg asfotase alfa 6 times per week or as 2 mg/kg asfotase alfa 3 times per week depending on the recommendation of your doctor. Each dose will be administered by injection under the skin (subcutaneous), (see the dosing chart below for detailed information on the volume to be injected, and the type of vials to be used, based on your weight).
- Doses will need to be adjusted regularly by your doctor as the body weight changes.
- The maximum volume per injection should not exceed 1 ml. If more than 1 ml is required, you need to do multiple injections immediately one after the other.

**If injecting 3 x per week**

| Body Weight (kg) | Volume to be injected | Color code of the vial to be used |
|---|---|---|
| **3** | 0.15 ml | Dark blue |
| **4** | 0.20 ml | Dark blue |
| **5** | 0.25 ml | Dark blue |
| **6** | 0.30 ml | Dark blue |
| **7** | 0.35 ml | Orange |
| **8** | 0.40 ml | Orange |
| **9** | 0.45 ml | Orange |
| **10** | 0.50 ml | Light blue |
| **11** | 0.55 ml | Light blue |
| **12** | 0.60 ml | Light blue |
| **13** | 0.65 ml | Light blue |
| **14** | 0.70 ml | Light blue |
| **15** | 0.75 ml | Pink |
| **16** | 0.80 ml | Pink |
| **17** | 0.85 ml | Pink |
| **18** | 0.90 ml | Pink |
| **19** | 0.95 ml | Pink |
| **20** | 1 ml | Pink |
| **25** | 0.50 ml | Green |
| **30** | 0.60 ml | Green |
| **35** | 0.70 ml | Green |
| **40** | 0.80 ml | Green |

**If injecting 6 x per week**

| Body Weight (kg) | Volume to be injected | Color code of the vial to be used |
|---|---|---|
| **6** | 0.15 ml | Dark blue |
| **7** | 0.18 ml | Dark blue |
| **8** | 0.20 ml | Dark blue |
| **9** | 0.23 ml | Dark blue |
| **10** | 0.25 ml | Dark blue |
| **11** | 0.28 ml | Dark blue |
| **12** | 0.30 ml | Dark blue |
| **13** | 0.33 ml | Orange |
| **14** | 0.35 ml | Orange |
| **15** | 0.38 ml | Orange |
| **16** | 0.40 ml | Orange |
| **17** | 0.43 ml | Orange |
| **18** | 0.45 ml | Orange |
| **19** | 0.48 ml | Light blue |
| **20** | 0.50 ml | Light blue |
| **25** | 0.63 ml | Light blue |
| **30** | 0.75 ml | Pink |
| **35** | 0.88 ml | Pink |
| **40** | 1 ml | Pink |
| **50** | 0.50 ml | Green |
| **60** | 0.60 ml | Green |
| **70** | 0.70 ml | Green |
| **80** | 0.80 ml | Green |
| **90** | 0.90 ml | Green (x2) |
| **100** | 1 ml | Green (x2) |

**Injection recommendations**

- You may experience a reaction at the injection site. Read section 4 carefully to know what side effects can occur before using this medicine
- When injecting regularly, the injection site should be changed between different areas of the body to help reduce potential pain and irritation
- Areas with a good amount of fat below the skin (thighs, arms (deltoids), abdomen, and buttocks) are the most suitable areas to inject. Please discuss with you doctor or nurse the best sites for you.

**Before injecting Strensiq, please read the following instructions carefully**

- Each vial is for single use and should only be punctured once. Strensiq liquid should look clear, slightly opalescent or opalescent, colourless to slightly yellow and may have a few small translucent or white particles in it. Do not use it if the liquid is discoloured or contains any

lumps or large particles in it and get a new vial. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

- If you are injecting this medicine yourself, you will be shown how to prepare and inject the medicine 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**

Step 1: Preparing the Strensiq dose

1. Wash your hands thoroughly with soap and water.
2. Take the unopened Strensiq vial(s) out of the refrigerator 15 to 30 minutes before injecting to allow the liquid to reach room temperature. Do not warm Strensiq in any other way (for example, do not warm it in a microwave or in hot water). Upon Removal of the vial(s) from refrigeration, Strensiq should be used within 3 hours maximum (see section 5. How to store Strensiq).
3. Remove the protective cap from the Strensiq vial(s). Remove the protective plastic from the syringe to be used.
4. Always use a new syringe contained in a protective plastic.
5. Place a larger bore needle (e.g. 25G) on the empty syringe and with the protective cap on, push down and turn clockwise the needle onto the syringe until it is tight.
6. Remove the plastic cap covering the syringe needle. Pay attention not to hurt yourself with the needle.
7. Pull the plunger back to draw air into the syringe equal to your dose.

Step 2: Withdrawing Strensiq solution from the vial


1. Holding the syringe and vial, insert the needle through the sterile rubber seal and into the vial.

2. Push the plunger in completely to inject air into the vial.

3. Invert the vial and syringe. With the needle in the solution, pull the plunger to withdraw the correct dose into the syringe.

4. Before removing the needle from the vial, check that the appropriate volume

has been withdrawn and check the syringe for air bubbles. In the event that bubbles appear in the syringe, hold the syringe with the needle pointing upwards and gently tap the side of the syringe until the bubbles rise to the top.

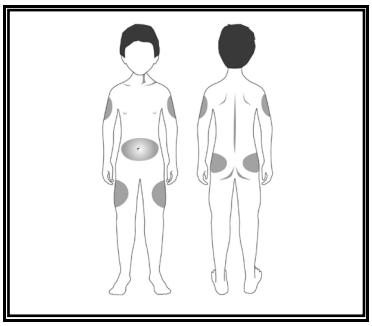
5. Once all the bubbles are at the top of the syringe, gently push on the plunger to force the bubbles out of the syringe and back into the vial.
6. After removing the bubbles, recheck the dose of medication in the syringe to be sure you have drawn up the correct amount. You may need to use several vials to withdraw the complete amount needed to reach the correct dose.

Step 3: Placing the needle for injection on the syringe

1. Remove the needle from the vial. Recap with one hand by placing the cap on a flat surface, slide the needle into the cap, lift it up and snap it on securely using only one hand.
2. Carefully remove the larger bore needle pushing down and turning counterclockwise. Dispose the needle with the protective cap in your sharps container.
3. Place a smaller bore needle (e.g. 27 or 29G) on the filled syringe and with the protective cap on, push down and turn clockwise the needle onto the syringe until it is tight. Pull the cap straight off the needle.
4. Hold the syringe with the needle pointing up and tap the barrel of the syringe with your finger to remove any air bubbles.

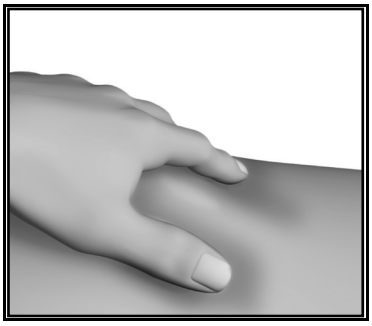
Control visually that the volume contained into the syringe is correct.
The volume per injection should not exceed 1 ml. If it is the case, multiple injections should be done at different sites.
You are now ready to inject the correct dose.

Step 4: Injecting Strensiq

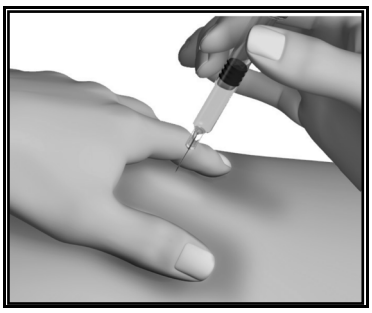


1. Choose an injection site (thighs, abdomen, arms (deltoids), buttocks). Most suitable areas for injection are marked grey in the picture. Your doctor will advise you on the possible injection sites

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

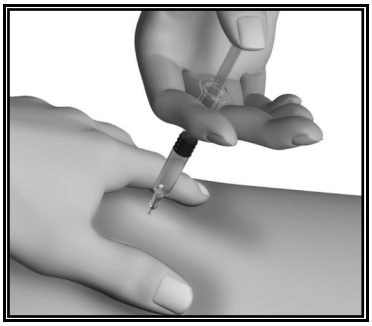


2. Gently pinch the skin of the chosen injection area between your thumb and index finger.



3. 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 fat under the skin or thin skin, a 45º angle may be preferable.



4. While continuing to hold the skin, push the syringe plunger to inject the medicine slowly, and steadily all the way in.

5. 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.

If you need a second injection for your prescribed dose, get another Strensiq vial and repeat steps 1 through 4.

Step 5: Disposing of supplies

Please collect your syringes, vials and needle in a sharps container. Your doctor, pharmacist or nurse will advise you on how you can obtain a sharps container.

**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 inject a double dose to make up for a forgotten dose and contact your doctor for advice.

For more information, please consult:

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

The most serious side effects seen in patients receiving asfotase alfa have been allergic reactions including life threatening allergic reactions requiring medical treatment similar to anaphylaxis. This

side effect is common [may affect up to 1 in 10 people]). Patients who experienced these serious allergic reactions had difficulty breathing, choking sensation, nausea, swelling around the eyes, and dizziness. The reactions occurred within minutes after using asfotase alfa and can occur in patients who were using asfotase alfa for more than one year. **If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately.**

Additionally, other allergic reactions (hypersensitivity) which may appear as redness (erythema), fever (pyrexia), rash, itchiness (pruritis), irritability, feeling sick (nausea), throwing up (vomiting), pain, chills (rigor), numbness of the mouth (hypoaesthesia oral), headache, blushing (flushing), fast beating of the heart (tachycardia), and cough may occur commonly . **If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately.**

**Very common: may affect more than 1 in 10 people**
Reactions at the injection site during the injection of the medicine or during the hours following the injection (which can lead to redness, discolorations, itching, pain, fatty lumps or decreased fatty tissue on the surface of the skin, skin hypopigmentation, and/or swelling)
Fever (pyrexia)
Irritability
Skin redness (erythema)
Pain in hands and feet (pain in extremity)
Bruise (contusion)
Headache

**Common: may affect up to 1 in 10 people**
Stretched skin, skin discolouration
Feeling sick (nausea)
Numbness of the mouth (hypoaesthesia oral)
Aching muscles (myalgia)
Scar
Increased tendency to bruise
Hot flush
Infection of skin at injection site (injection site cellulitis)
Reduced levels of calcium in the blood (hypocalcaemia)
Kidney stones (nephrolithiasis)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Strensiq

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.
After opening the vial, the product should be used immediately (within 3 hours maximum at room temperature, between 23°C and 27°C).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Strensiq contains**
The active substance is asfotase alfa. Each ml of solution contains 40 mg of asfotase alfa.
Each vial of 0.3 ml solution (40 mg/ml) contains 12 mg of asfotase alfa.
Each vial of 0.45 ml solution (40 mg/ml) contains 18 mg of asfotase alfa.
Each vial of 0.7 ml solution (40 mg/ml) contains 28 mg of asfotase alfa.
Each vial of 1 ml solution (40 mg/ml) contains 40 mg of asfotase alfa.

The other ingredients are sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate and water for injections.

**What Strensiq looks like and contents of the pack**
Strensiq is presented as a clear, slightly opalescent or opalescent, colourless to slightly yellow aqueous solution for injection in vials containing 0.3 ml, 0.45 ml, 0.7 ml and 1 ml of solution. A few small translucent or white particles may be present.

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

**Marketing Authorisation Holder**
Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

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

**This leaflet was last revised in**

This medicine has been authorised under ‘exceptional circumstances’.
This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

**Package leaflet: Information for the user**

**Strensiq 100 mg/ml solution for injection**
**(80 mg/0.8 ml)**
asfotase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Strensiq is and what it is used for

**What is Strensiq**
Strensiq is a medicine used to treat the inherited disease hypophosphatasia that started in childhood. It contains the active substance asfotase alfa.

**What is hypophosphatasia**
Patients with hypophosphatasia have low levels of an enzyme called alkaline phosphatase that is important for various body functions, including the proper hardening of bones and teeth. Patients have problems with bone growth and strength, which can lead to broken bones, bone pain, and difficulty walking, as well as difficulties with breathing and a risk of seizures (fits).

**What is Strensiq used for**
The active substance in Strensiq can replace the missing enzyme (alkaline phosphatase) in hypophosphatasia. It is used for long-term enzyme replacement treatment to manage symptoms.

**What benefits of Strensiq have been shown in clinical studies**
Strensiq has shown benefits for patients' mineralization of the skeleton and growth.

## 2. What you need to know before you use Strensiq

**Do not use Strensiq**
If you are severely allergic to asfotase alfa (see section 'Warnings and precautions' below) or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor before using Strensiq.

- Patients receiving asfotase alfa have had allergic reactions including life threatening allergic reactions requiring medical treatment similar to anaphylaxis. Patients who experienced anaphylaxis-like symptoms had 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.
  Should you experience anaphylactic reaction, or an event with similar symptoms, your doctor will discuss with you the next steps and the possibility to restart Strensiq under medical supervision. Always follow the instructions provided by your doctor.
- The development of blood proteins against Strensiq, also called anti-drug antibodies, may occur during the treatment. Talk to your doctor if you experience decreased efficacy with Strensiq.
- Fatty lumps or decreased fatty tissue on the surface of the skin (localized lipodystrophy) have been reported at injection sites after several months in patients using Strensiq. Read section 3 carefully to know the injection recommendations. This is important to rotate the injection from among the following sites to reduce the risk of lipodystrophy: abdominal area, thigh, or deltoid.
- In studies, some eye-related side-effects (e.g. calcium buildup on the eye [conjunctival and corneal calcification]) have been reported both in patients using Strensiq and those who were not, probably associated with hypophosphatasia. Talk to your doctor in case of problems with your vision.
- Early fusion of the bones of the head (craniosynostosis) 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.
- If you are treated with Strensiq, you may experience a reaction at the injection site (pain, nodule, rash, discoloration) during the injection of the medicine or during the hours following the injection. If you experience any severe reaction at the injection site, tell your doctor immediately.
- Increase of parathyroid hormone concentration and low calcium levels have been reported in studies. As a consequence, your doctor may ask you to take supplements of calcium and oral vitamin D if needed.
- Weight gain may occur during your treatment with Strensiq. Your doctor will provide dietary advice as necessary.

**Other medicines and Strensiq**
Tell your doctor or pharmacist if you are using, have recently used or might use any other 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.

**Pregnancy**
Strensiq should not be used during pregnancy. The use of effective birth control during treatment should be considered in women who are able to get pregnant.

**Breast-feeding**
It is not known whether Strensiq can pass into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Strensiq, considering the benefit of breast-feeding to the baby and the benefit of Strensiq to the mother.

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**
This medicine is not expected to have any effect on the ability to drive or use machines.

**Important information about some of the ingredients of Strensiq**
This medicine contains less than 1 mmol sodium (23 mg) per vial, which means it is essentially 'sodium-free'.

## 3. How to use Strensiq

Always use this medicine exactly as described in this leaflet or as your doctor, or pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.
How to use Strensiq will be explained to you by a doctor who is experienced in the management of patients with metabolic or bone related diseases. After being trained by the doctor or specialized nurse, you can inject Strensiq yourself at home.

**Dose**
- The dose you receive is based on your body weight.
- The correct dose will be calculated by your doctor and consists of a total of 6 mg of asfotase alfa per kg of body weight every week, given either as an injection of 1 mg/kg asfotase alfa 6 times per week or as 2 mg/kg asfotase alfa 3 times per week depending on the recommendation of your doctor. Each dose will be administered by injection under the skin (subcutaneous), (see the dosing chart below for detailed information on the volume to be injected, and the type of vials to be used, based on your weight).
- Doses will need to be adjusted regularly by your doctor as the body weight changes.
- The maximum volume per injection should not exceed 1 ml. If more than 1 ml is required, you need to do multiple injections immediately one after the other.

**If injecting 3x per week**

| Body Weight (kg) | Volume to be injected | Color code of the vial to be used |
|---|---|---|
| **3** | 0.15 ml | Dark blue |
| **4** | 0.20 ml | Dark blue |
| **5** | 0.25 ml | Dark blue |
| **6** | 0.30 ml | Dark blue |
| **7** | 0.35 ml | Orange |
| **8** | 0.40 ml | Orange |
| **9** | 0.45 ml | Orange |
| **10** | 0.50 ml | Light blue |
| **11** | 0.55 ml | Light blue |
| **12** | 0.60 ml | Light blue |
| **13** | 0.65 ml | Light blue |
| **14** | 0.70 ml | Light blue |
| **15** | 0.75 ml | Pink |
| **16** | 0.80 ml | Pink |
| **17** | 0.85 ml | Pink |
| **18** | 0.90 ml | Pink |
| **19** | 0.95 ml | Pink |
| **20** | 1 ml | Pink |
| **25** | 0.50 ml | Green |
| **30** | 0.60 ml | Green |
| **35** | 0.70 ml | Green |
| **40** | 0.80 ml | Green |

**If injecting 6 x per week**

| Body Weight (kg) | Volume to be injected | Color code of the vial to be used |
|---|---|---|
| **6** | 0.15 ml | Dark blue |
| **7** | 0.18 ml | Dark blue |
| **8** | 0.20 ml | Dark blue |
| **9** | 0.23 ml | Dark blue |
| **10** | 0.25 ml | Dark blue |
| **11** | 0.28 ml | Dark blue |
| **12** | 0.30 ml | Dark blue |
| **13** | 0.33 ml | Orange |
| **14** | 0.35 ml | Orange |
| **15** | 0.38 ml | Orange |
| **16** | 0.40 ml | Orange |
| **17** | 0.43 ml | Orange |
| **18** | 0.45 ml | Orange |
| **19** | 0.48 ml | Light blue |
| **20** | 0.50 ml | Light blue |
| **25** | 0.63 ml | Light blue |
| **30** | 0.75 ml | Pink |
| **35** | 0.88 ml | Pink |
| **40** | 1 ml | Pink |
| **50** | 0.50 ml | Green |
| **60** | 0.60 ml | Green |
| **70** | 0.70 ml | Green |
| **80** | 0.80 ml | Green |
| **90** | 0.90 ml | Green (x2) |
| **100** | 1 ml | Green (x2) |

**Injection recommendations**

- You may experience a reaction at the injection site. Read section 4 carefully to know what side effects can occur before using this medicine
- When injecting regularly, the injection site should be changed between different areas of the body to help reduce potential pain and irritation
- Areas with a good amount of fat below the skin (thighs, arms (deltoids), abdomen, and buttocks) are the most suitable areas to inject. Please discuss with you doctor or nurse the best sites for you.

**Before injecting Strensiq, please read the following instructions carefully**

- Each vial is for single use and should only be punctured once. Strensiq liquid should look clear, slightly opalescent or opalescent, colourless to slightly yellow and may have a few small translucent or white particles in it. Do not use it if the liquid is discoloured or contains any

lumps or large particles in it and get a new vial. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

- If you are injecting this medicine yourself, you will be shown how to prepare and inject the medicine 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:**

Step 1: Preparing the Strensiq dose

1. Wash your hands thoroughly with soap and water.
2. Take the unopened Strensiq vial(s) out of the refrigerator 15 to 30 minutes before injecting to allow the liquid to reach room temperature. Do not warm Strensiq in any other way (for example, do not warm it in a microwave or in hot water). Upon removal of the vial(s) from refrigeration, Strensiq should be used within 3 hours maximum (see section 5. How to store Strensiq).
3. Remove the protective cap from the Strensiq vial(s). Remove the protective plastic from the syringe to be used.
4. Always use a new syringe contained in a protective plastic.
5. Place a larger bore needle (e.g. 25G) on the empty syringe and with the protective cap on, push down and turn clockwise the needle onto the syringe until it is tight.
6. Remove the plastic cap covering the syringe needle. Pay attention not to hurt yourself with the needle.
7. Pull the plunger back to draw air into the syringe equal to your dose.

Step 2: Withdrawing Strensiq solution from the vial


1. Holding the syringe and vial, insert the needle through the sterile rubber seal and into the vial.

2. Push the plunger in completely to inject air into the vial.

3. Invert the vial and syringe. With the needle in the solution, pull the plunger to withdraw the correct dose into the syringe.

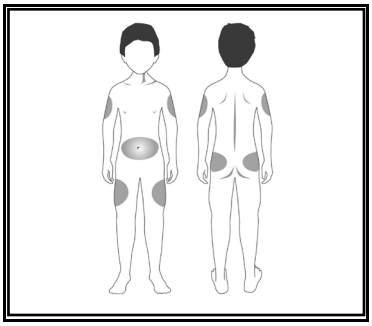
4. Before removing the needle from the vial, check that the appropriate volume has been withdrawn and check the syringe for air bubbles. In the event that bubbles appear in the syringe, hold the syringe with the needle pointing upwards and gently tap the side of the syringe until the bubbles rise to the top.
5. Once all the bubbles are at the top of the syringe, gently push on the plunger to force the bubbles out of the syringe and back into the vial.
6. After removing the bubbles, recheck the dose of medication in the syringe to be sure you have drawn up the correct amount. You may need to use several vials to withdraw the complete amount needed to reach the correct dose.

Step 3: Placing the needle for injection on the syringe

1. Remove the needle from the vial.Recap with one hand by placing the cap on a flat surface, slide the needle into the cap, lift it up and snap it on securely using only one hand.
2. Carefully, remove the larger bore needle pushing down and turning counterclockwise. Dispose the needle with the protective cap in your sharps container.
3. Place a smaller bore needle (e.g. 27 or 29G) on the filled syringe and with the protective cap on, push down and turn clockwise the needle onto the syringe until it is tight. Pull the cap straight off the needle.
4. Hold the syringe with the needle pointing up and tap the barrel of the syringe with your finger to remove any air bubbles.

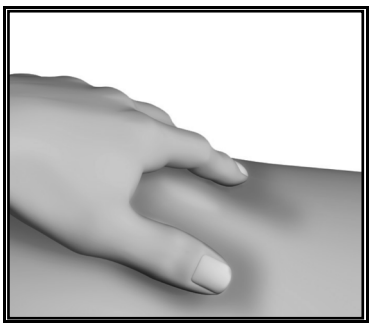
Control visually that the volume contained into the syringe is correct.
The volume per injection should not exceed 1 ml. If it is the case, multiple injections should be done at different sites.
You are now ready to inject the correct dose.

Step 4: Injecting Strensiq

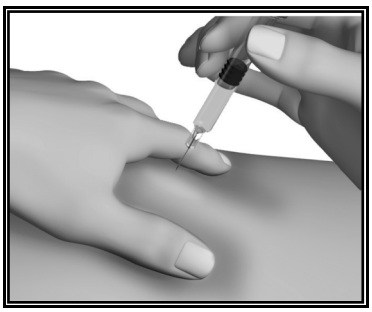


1. Choose an injection site (thighs, abdomen, arms (deltoids), buttocks). Most suitable areas for injection are marked grey in the picture. Your doctor will advise you on the possible injection sites.

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

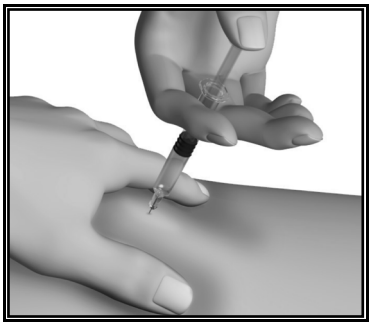


2. Gently pinch the skin of the chosen injection area between your thumb and index finger.



3. 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 fat under the skin or thin skin, a 45º angle may be preferable.



4. While continuing to hold the skin, push the syringe plunger to inject the medicine slowly, and steadily all the way in.

5. 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.

If you need a second injection for your prescribed dose, get another Strensiq vial and repeat steps 1 through 4.

Step 5: Disposing of supplies

Please collect your syringes, vials and needle in a sharps container. Your doctor, pharmacist or nurse will advise you on how you can obtain a sharps container.

**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 inject a double dose to make up for a forgotten dose and contact your doctor for advice.

For more information, please consult:

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

The most serious side effects seen in patients receiving asfotase alfa have been allergic reactions including life threatening allergic reactions requiring medical treatment similar to anaphylaxis. This

side effect is common [may affect up to 1 in 10 people]). Patients who experienced these serious allergic reactions had difficulty breathing, choking sensation, nausea, swelling around the eyes, and dizziness. The reactions occurred within minutes after using asfotase alfa and can occur in patients who were using asfotase alfa for more than one year. **If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately.**

Additionally, other allergic reactions (hypersensitivity) which may appear as redness (erythema), fever (pyrexia), rash, itchiness (pruritis), irritability, feeling sick (nausea), throwing up (vomiting), pain, chills (rigor), numbness of the mouth (hypoaesthesia oral), headache, blushing (flushing), fast beating of the heart (tachycardia), and cough may occur commonly. **If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately.**

**Very common: may affect more than 1 in 10 people**
Reactions at the injection site during the injection of the medicine or during the hours following the injection (which can lead to redness, discolorations, itching, pain, fatty lumps or decreased fatty tissue on the surface of the skin, skin hypopigmentation, and/or swelling)
Fever (pyrexia)
Irritability
Skin redness (erythema)
Pain in hands and feet (pain in extremity)
Bruise (contusion)
Headache

**Common: may affect up to 1 in 10 people**
Stretched skin, skin discolouration
Feeling sick (nausea)
Numbness of the mouth (hypoaesthesia oral)
Aching muscles (myalgia)
Scar
Increased tendency to bruise
Hot flush
Infection of skin at injection site (injection site cellulitis)
Reduced levels of calcium in the blood (hypocalcaemia)
Kidney stones (nephrolithiasis)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Strensiq

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.
After opening the vial, the product should be used immediately (within 3 hours maximum at room temperature, between 23°C and 27°C).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Strensiq contains**
The active substance is asfotase alfa. Each ml of solution contains 100 mg of asfotase alfa.
Each vial of 0.8 ml solution (100 mg/ml) contains 80 mg of asfotase alfa.

The other ingredients are sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate and water for injections.

**What Strensiq looks like and contents of the pack**
Strensiq is presented as a clear, slightly opalescent or opalescent, colourless to slightly yellow aqueous solution for injection in vials containing 0.8 ml of solution. A few small translucent or white particles may be present.

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

**Marketing Authorisation Holder**
Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

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

**This leaflet was last revised in**

This medicine has been authorised under ‘exceptional circumstances’.
This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.