

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, colourless to slightly yellow, aqueous solution; pH 7.4.

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.

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)

Renal and hepatic impairment

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

Adult patients

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

Elderly

There is no evidence for special considerations when Strensiq is administered to elderly 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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity, anaphylaxis or anaphylactoid reactions have not been observed with asfotase alfa in any clinical trials. Severe allergic-type hypersensitivity reactions are possible, including urticaria, difficulty breathing and/or cardiovascular collapse. 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. There have been no adverse reactions related to anti-asfotase alfa antibody status in clinical trials.

Furthermore, patients confirmed positive for anti-drug antibodies have not shown signs of hypersensitivity or tachyphylaxis with asfotase alfa administration.

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 usually helps to effectively manage these reactions. These have been generally assessed as non-serious, mild to moderate in severity and self-limiting.

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

Craniosynostosis

In asfotase alfa clinical studies adverse events of craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis 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 Strensiq 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. Periodic ophthalmology examination and renal ultrasounds are recommended 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no 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.

Breast-feeding should be discontinued during treatment with asfotase alfa.

Fertility

Preclinical fertility studies were conducted and showed no evidence of effect on fertility and embryo-fetal development.

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

The most common adverse reactions observed were injection site reactions and injection-associated adverse reactions. Most of these reactions were non-serious, mild to moderate in intensity. Serious injection-associated reactions were reported in 2 patients with no discontinuation of asfotase alfa treatment: 1 patient with infantile-onset hypophosphatasia recorded fever and chills, and in 1 patient with juvenile-onset hypophosphatasia recorded hypoaesthesia oral, pain in extremity, chills, and headache.

Tabulated list of adverse reactions

Table 1 gives the adverse reactions observed from clinical trials in 71 patients (age 1 day to 66 years). Adverse reactions with asfotase alfa are listed by system organ class and preferred term using MedDRA frequency convention very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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 (age 1 day to 66 years)

System Organ Class	Frequency category	Adverse reaction
Infections and infestations	common	Injection site cellulitis
Blood and lymphatic system disorders	common	Increased tendency to bruise
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	Lipohypertrophy Cutis Laxa Skin discolouration including hypopigmentation Skin disorder (stretched skin)
Musculoskeletal and connective tissue disorders	very common	Pain in extremity
	common	Myalgia
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

Description of selected adverse reactions

Injection site reactions

Injection site reactions (including injection site erythema, discolouration, pain, pruritus, macule, swelling, bruising, hypertrophy, induration, reaction, atrophy, nodule, rash, papule, haematoma, inflammation, urticarial, warmth, haemorrhage, cellulitis and mass) are the most common adverse reactions observed in about 73% of the patients in clinical studies. The frequency of injection site reactions was higher in patients with juvenile-onset hypophosphatasia and in patients who received

injections 6 times/week (compared to 3 times/week). Most injection site reactions were mild and self-limiting, and none was reported as a serious adverse event. Two patients experienced injection site reactions that led to reductions of their asfotase alfa dose.

One patient out of 71 patients treated in clinical trials experienced a severe injection site reaction of injection site discolouration which led to the discontinuation of treatment.

Immunogenicity

There is potential for immunogenicity. Among 69 hypophosphatasia patients enrolled in the clinical trials and who have post baseline data, 56 (81.2%) tested positive for anti-drug antibodies at some time point after receiving Strensiq treatment. Among those 56 patients, 25 (44.6%) also showed the presence of neutralizing antibodies. The antibody response (with or without presence of neutralizing antibodies) was time variant in nature. The development of antibodies has not been shown to affect clinical efficacy or safety (see section 5.2).

No trends in adverse events based on antibody status were observed in clinical trials. Furthermore, patients confirmed positive for antibodies have not shown signs of hypersensitivity or tachyphylaxis following subcutaneous administration of asfotase alfa.

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 no experience with overdose of asfotase alfa. For management of adverse reactions, see sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: <not yet assigned>, ATC code: <not yet assigned>

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, non-randomised study. 13 patients were enrolled. 5 patients presented with 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. 12 patients are on-going in the study. The study employed historical controls from the same centre as patients who received asfotase alfa and who had been subject to a similar protocol of clinical management.

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 physal widening, metaphyseal flaring, irregularity of provisional zone of calcification, metaphyseal radiolucencies, metadiaphyseal sclerosis, osteopenia, 'popcorn' calcification in metadiaphysis, demineralization of distal metaphysis, transverse subphysal band of lucency and tongues of radiolucency. X-ray changes from baseline were then rated using the Radiographic Global Impression of Change rating scale as follows: -3=severe worsening, -2=moderate worsening, -1=minimal worsening, 0=no change, +1=minimal healing, +2=substantial healing, +3=near-complete or complete healing. Patients who received asfotase alfa moved to scores of +2 and +3 over the first 6 months of exposure and this was sustained with on-going treatment. Historical controls did not show change over time.

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: 9/13 patients displayed persistent apparent catch-up height-gain as shown by movement over time to a higher percentile on CDC growth charts.

3/13 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 and 9 patients are on-going in the study. Onset of hypophosphatasia was under 6 months in all patients. Age at inclusion in the study was between 0.5 to 35 months.

7/11 patients in the full analysis set achieved Radiographic Global Impression of Change scores of +2 at Week 24 compared to baseline radiographs.

5/11 subjects displayed apparent catch-up height-gain. Fluctuation in height-gain was apparent and may reflect the more severe disease and higher rate of morbidity in these younger patients.

Study ENB-009-10

Study ENB-009-10 was an open-label, non-randomised study. 19 patients were enrolled and 18 patients are on-going in the study. Onset of hypophosphatasia was under 6 months in 4 patients, between 6 months and 18 years in 12 patients and over 18 years in 2 patients. Age of onset was not known for 1 patient. Age at inclusion was from 13 to 66 years.

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 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 (26 patients), both open-label, non-randomised, non-controlled studies of patients aged 0.1 to 310 weeks at baseline, 21 of 37 patients required ventilation support:

- 14 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 ventilation (time on ventilation from 24 to 168 weeks), all had achieved an RGI-C score ≥ 2
 - 3 patients continued with ventilation support, RGI-C score ≤ 2
 - 3 patients died whilst on ventilation support
 - 1 patient withdrew consent
- 7 patients started non-invasive ventilation (BiPAP or CPAP) after baseline (2 patients required brief support with invasive ventilation).
 - 5 patients were weaned off ventilation (time on ventilation from 4 weeks to 48 weeks)
 - 2 patients died

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Strensiq in one or more subsets of the paediatric population in hypophosphatasia (see section 4.2 for information on paediatric use).

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 (AUC_{τ}) 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) AUC_{τ} 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 \pm SD elimination half-life following subcutaneous administration was 2.28 ± 0.58 days.

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

15 months

Chemical and physical in-use stability has been demonstrated for up to 1 hour 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 before administration of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml vial (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: cartons 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
1-15, Avenue Edouard Belin
92500 Rueil-Malmaison
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

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 Trading
Park West, Block 10A, Nangor Road
Dublin 12
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**

The requirements for submission of periodic safety update reports 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 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 reactions.

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:

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

The Patient/parents or caregivers guides 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
- 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

• **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
<p>The MAH should conduct a multicentre, randomized, open-label, Phase 2a study of Strensiq in patients with hypophosphatasia (HPP) to:</p> <p>(i) evaluate pharmacokinetics (PK) of Strensiq in adults following administration of the dose advised in children;</p> <p>(ii) provide dose response data on plasma inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP) and to explore evidence of clinical benefit.</p> <p>In order to ensure that the data are reliable, the MAH should submit a study protocol including acceptable techniques for blood collection, storage and assay for the PPi and PLP biomarkers, to be agreed by CHMP before the start of the study.</p>	31 March 2017
<p>The MAH should extend the studies ENB-008-10 and ENB-009-10 to provide efficacy data (such as, but not limited to RGI-C scores, height and weight change, biomarkers measurement) in patients 13 to 18 year-old of age.</p>	31 March 2017

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
<p>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.</p>	<p>Annually within annual reassessment</p>

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/1.0 ml).

3. 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; 1.0] ml
12 vials of 0.3[0.45; 0.7; 1.0] 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
1-15, Avenue Edouard Belin
92500 Rueil-Malmaison
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/1.0 ml

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/1.0 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

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
1-15, Avenue Edouard Belin
92500 Rueil-Malmaison
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

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/1.0 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
2. What you need to know before you use Strensiq
3. How to use Strensiq
4. Possible side effects
5. How to store Strensiq
6. Contents of the pack and other information

1. What Strensiq is and what it is used for

What is Strensiq

Strensiq is a medicine used to treat the inherited disease hypophosphatasia. 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 allergic to asfotase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

- Strensiq may cause allergic reactions in some people. Symptoms of such reactions include vomiting, difficulty breathing, fast heart rate, sudden fall in blood pressure, hives or rash. If you

experience any of these symptoms, tell your doctor immediately. You may need to be given additional medicines to prevent an allergic reaction (antihistamines or corticosteroids).

- In studies, some eye-related side-effects 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 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.

Pregnancy and breast-feeding

Strensiq should not be used during pregnancy or breast-feeding unless medically necessary.

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.

Dosage

- 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, 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).
- This total dose can be 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.
- 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	1.00 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	1.00 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	1.00 ml	Green (x2)

Use in children and adolescents

As in adults, the recommended dosage of Strensiq in children and adolescents is 6 mg of asfotase alfa per kg weekly. Doses will need to be adjusted regularly by your doctor as the body weight changes.

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 (thigh, arm) are the most suitable areas to inject. Please discuss with your 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. Only clear and colourless to slightly yellow aqueous solution without visible signs of deterioration should be used. Any unused medicinal product or waste material should be disposed of immediately.
- 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:

Wash your hands thoroughly with soap and water.

Remove the protective cap from the Strensiq vial.

After removal from the refrigerator Strensiq should be used within 1 hour maximum

Remove the protective plastic from the syringe to be used.

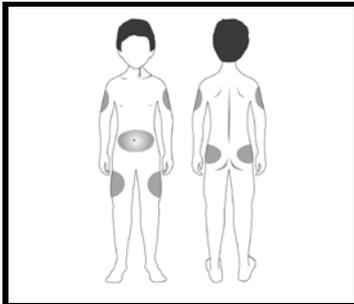
Always use a new syringe contained in a protective plastic.

Pay attention not to hurt yourself with the needle.

Withdraw the correct dose of Strensiq into the syringe. You may need to use several vials to withdraw the complete amount needed to reach the correct dose.

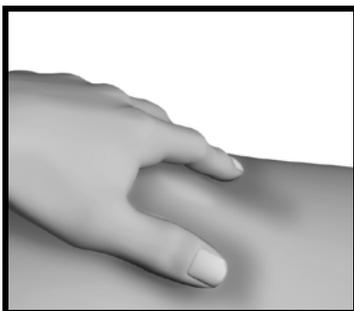
Control visually that the volume contained into the syringe is correct.

The volume per injection should not exceed 1 ml. If it is the case, multiple injections should be done at different sites.

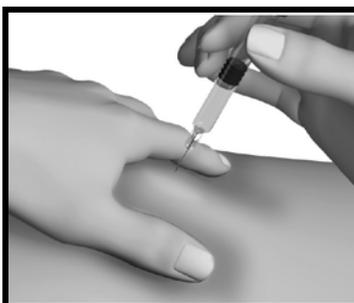


Choose an injection site (thighs, abdomen, arms, buttocks). Most suitable areas for injection are marked grey in the picture. Your doctor will advise you on the possible injection sites

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

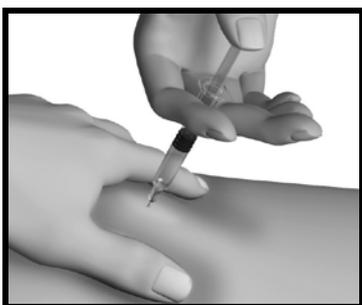


Gently pinch the skin of the chosen injection area between your thumb and index finger.



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

For patients who have little fat under the skin or thin skin, a 45° angle may be preferable.



While continuing to hold the skin, push the syringe plunger to inject the medicine while counting slowly to 10.

Remove the needle, release the skin fold and gently place a piece of cotton wool or gauze over the injection site for a few seconds.

This will help seal the punctured tissue and prevent any leakage. Do not rub the injection site after injection. 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 accidentally 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: asfotasealfa-patienteducation.co.uk



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.

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, and/or swelling)

Fever (pyrexia), irritability

Skin redness (erythema)

Pain in hands and feet

Contusion (bruise)

Headache

Common: may affect up to 1 in 10 people

Chills

Fatty lumps on the surface of the skin (lipohypertrophy), loose skin (cutis laxa), stretched skin, skin discoloration including a lighter area of the skin (skin hypopigmentation)

Feeling sick (nausea), numbness of the mouth (hypoesthesia oral)

Aching muscles (myalgia)

Scar

Increased tendency to bruise

Hot flush

Infection of skin at injection site (injection site cellulitis)

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 1 hour maximum).

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 1.0 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 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.

Pack sizes of 1 or 12 vials.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

Alexion Europe SAS

1-15, Avenue Edouard Belin

92500 Rueil-Malmaison

France

Phone: +33 1 47 32 36 03

Manufacturer

Alexion Pharma International Trading

Park West, Block 10A, Nangor Road

Dublin 12

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
2. What you need to know before you use Strensiq
3. How to use Strensiq
4. Possible side effects
5. How to store Strensiq
6. Contents of the pack and other information

1. What Strensiq is and what it is used for

What is Strensiq

Strensiq is a medicine used to treat the inherited disease hypophosphatasia. 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 allergic to asfotase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

- Strensiq may cause allergic reactions in some people. Symptoms of such reactions include vomiting, difficulty breathing, fast heart rate, sudden fall in blood pressure, hives or rash. If you

experience any of these symptoms, tell your doctor immediately. You may need to be given additional medicines to prevent an allergic reaction (antihistamines or corticosteroids).

- In studies, some eye-related side-effects 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 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 as necessary.

Other medicines and Strensiq

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

Pregnancy and breast-feeding

Strensiq should not be used during pregnancy or breast-feeding unless medically necessary.

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.

Dosage

- 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, 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).
- This total dose can be 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.
- 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	1.00 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	1.00 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	1.00 ml	Green (x2)

Use in children and adolescents

As in adults, the recommended dosage of Strensiq in children and adolescents is 6 mg of asfotase alfa per kg weekly. Doses will need to be adjusted regularly by your doctor as the body weight changes.

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 (thigh, arm) are the most suitable areas to inject. Please discuss with your 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. Only clear and colourless to slightly yellow aqueous solution without visible signs of deterioration should be used. Any unused medicinal product or waste material should be disposed of immediately.
- 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:

Wash your hands thoroughly with soap and water.

Remove the protective cap from the Strensiq vial.

After removal from the refrigerator Strensiq should be used within 1 hour maximum

Remove the protective plastic from the syringe to be used.

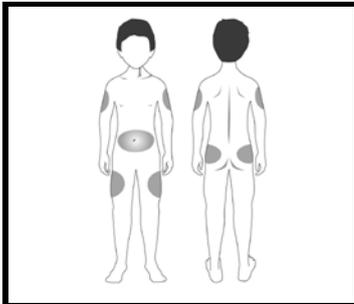
Always use a new syringe contained in a protective plastic.

Pay attention not to hurt yourself with the needle.

Withdraw the correct dose of Strensiq into the syringe. You may need to use several vials to withdraw the complete amount needed to reach the correct dose.

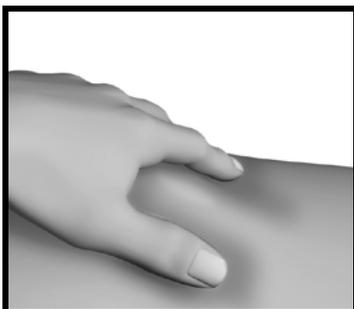
Control visually that the volume contained into the syringe is correct.

The volume per injection should not exceed 1 ml. If it is the case, multiple injections should be done at different sites.

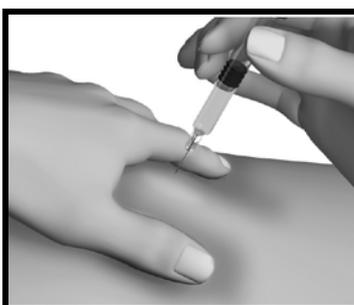


Choose an injection site (thighs, abdomen, arms, buttocks). Most suitable areas for injection are marked grey in the picture. Your doctor will advise you on the possible injection sites

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

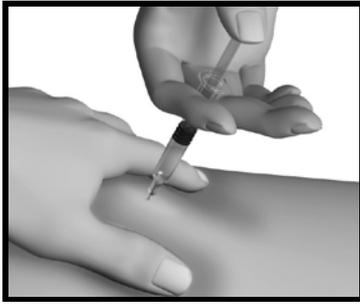


Gently pinch the skin of the chosen injection area between your thumb and index finger.



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

For patients who have little fat under the skin or thin skin, a 45° angle may be preferable.



While continuing to hold the skin, push the syringe plunger to inject the medicine while counting slowly to 10.

Remove the needle, release the skin fold and gently place a piece of cotton wool or gauze over the injection site for a few seconds.

This will help seal the punctured tissue and prevent any leakage. Do not rub the injection site after injection. 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 accidentally 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: asfotasealfa-patienteducation.co.uk



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.

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, and/or swelling)

Fever (pyrexia), irritability

Skin redness (erythema)

Pain in hands and feet

Contusion (bruise)

Headache

Common: may affect up to 1 in 10 people

Chills

Fatty lumps on the surface of the skin (lipohypertrophy), loose skin (cutis laxa), stretched skin, skin discoloration including a lighter area of the skin (skin hypopigmentation)

Feeling sick (nausea), numbness of the mouth (hypoesthesia oral)

Aching muscles (myalgia)

Scar

Increased tendency to bruise

Hot flush

Infection of skin at injection site (injection site cellulitis)

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 1 hour maximum).

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 colourless to slightly yellow aqueous solution for injection in vials containing 0.8 ml of solution.

Pack sizes of 1 or 12 vials.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

Alexion Europe SAS

1-15, Avenue Edouard Belin

92500 Rueil-Malmaison

France

Phone: +33 1 47 32 36 03

Manufacturer

Alexion Pharma International Trading

Park West, Block 10A, Nangor Road

Dublin 12

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.

Annex IV

Conclusions on the granting of the marketing authorisation under exceptional circumstances presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.