AUSTRALIAN PRODUCT INFORMATION – STRENSIQ® (ASFOTASE ALFA *RCH*) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

asfotase alfa *rch*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Strensiq is supplied as a single-use vial containing 40 or 100 mg/mL of asfotase alfa *rch*.

Asfotase alfa *rch* is a human recombinant tissue-nonspecific alkaline phosphatase (TNSALP) - Fc-deca-aspartate fusion protein with enzymatic activity, produced by recombinant DNA technology using mammalian Chinese Hamster Ovary (CHO) cell culture.

For the full list of excipients, see Section 6.1 - List of Excipients.

3 PHARMACEUTICAL FORM

Solution for injection. Strensiq is a sterile, preservative-free, non-pyrogenic, clear, slightly opalescent or opalescent, colourless to slightly yellow aqueous solution; few small translucent or white particles may be present. For subcutaneous injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Strensiq (asfotase alfa *rch*) is indicated as enzyme replacement therapy in patients with paediatric-onset hypophosphatasia.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Patient Monitoring Program: Physicians should enrol consenting patients receiving Strensiq in a monitoring program.

Recommended Dose

The recommended dosage regimen is 2 mg/kg of body weight, administered subcutaneously 3 times per week, or 1 mg/kg of body weight administered 6 times per week. Refer also to the dosing chart below.

The maximum volume of subcutaneous injection is 1 mL per injection site. If more than 1 mL is required, split the volume equally between two or more syringes, and administer each injection using a separate site.

Body Weight (kg)	Dose to be injected	
	If injecting 3x per week	If injecting 6x per week
3	6 mg	3mg
4	8 mg	4mg
5	10 mg	5mg
6	12 mg	6 mg
7	14 mg	7 mg
8	16 mg	8 mg
9	18 mg	9 mg
10	20 mg	10 mg
11	22 mg	11 mg
12	24 mg	12 mg
13	26 mg	13 mg
14	28 mg	14 mg
15	30 mg	15 mg
16	32 mg	16 mg
17	34 mg	17 mg
18	36 mg	18 mg
19	38 mg	19 mg
20	40 mg	20 mg
25	50 mg	25 mg
30	60 mg	30 mg
35	70 mg	35 mg
40	80 mg	40 mg
50	100 mg	50 mg
60	120 mg	60 mg
70	140 mg	70 mg
80	160 mg	80 mg
90	180 mg	90 mg
100	200 mg	100 mg

Patients should be regularly reviewed for their response to treatment and appropriate dose, including patients who have progressed to adolescence and adulthood.

Method of Administration

Patients can self-inject only if they have been appropriately trained on administration procedures.

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).

Strensiq should be administered using sterile disposable syringes and injection needles. The use of two different gauge needles is recommended, a larger bore needle (e.g. 25 gauge) for withdrawal of the medication and a smaller bore needle (e.g. 29 gauge) for

the injection. An aseptic technique should be used. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

Do not administer intravenously or intramuscularly. **Strensiq must be administered as subcutaneous injection.**

Do not administer injections in areas that are reddened, inflamed, or swollen. Injections sites should be rotated and carefully monitored for signs of potential reactions. Rotate the injection from among the following sites to reduce the risk of lipodystrophy: abdominal area, thigh, deltoid or buttocks (see Section 4.4- Special Warnings and Precautions for Use).

Special Populations

Patients with renal and hepatic impairment: the safety and efficacy of Strensiq have not been studied in patients with renal or hepatic impairment, and no specific dose regimen can be recommended for these patients.

Adult patients: safety and efficacy data in patients >18 years old are limited.

4.3 CONTRAINDICATIONS

Strensiq is contraindicated in patients with known hypersensitivity to asfotase alfa *rch*, Chinese hamster ovary cell proteins or to any of the excipients of this product.

Severe and life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable (see Section 4.4 – Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Limited Data

Due to HPP being an ultra-rare (orphan) disease, only limited, Phase II data have been provided in support of the safety and efficacy of Strensiq in the treatment of HPP.

Hypersensitivity

Hypersensitivity reactions have been reported in Strensiq-treated patients including signs and symptoms consistent with anaphylaxis. Signs and symptoms included difficulty breathing, choking sensation, periorbital oedema and dizziness. The reactions have occurred within minutes after subcutaneous administration of Strensiq. Hypersensitivity reactions have been observed as late as more than one year after treatment initiation. Other hypersensitivity reactions included vomiting, nausea, fever, headache, flushing, irritability, chills, erythema, rash, pruritus and oral hypoesthesia (see section 4.8 Adverse Effects (Undesirable Effects)).

Other severe allergic type hypersensitivity reactions are possible, including urticaria, difficulty breathing and/or cardiovascular collapse. If severe hypersensitivity reaction occurs, immediate discontinuation of Strensiq 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 Strensiq 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.

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable (see Section 4.3 - Contraindications).

Injection Site Reactions

Administration of Strensiq may result in local injection site reactions (including, but not limited to, erythema, rash, discolouration, pruritus, pain, papule, nodule or atrophy) defined as any related adverse event occurring during the injection, or until the end of the injection day (see Section 4.8 - Adverse Effects (Undesirable Effects)). These have been generally assessed as non-serious, mild to moderate in severity and self-limiting. Rotation of injection sites may help to minimise these reactions. One patient treated in clinical trials experienced a severe ISR of injection site discolouration which led to the discontinuation of Strensiq.

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 Strensiq in clinical trials. Patients should be advised to follow proper injection technique and to rotate injection sites (see Section 4.2 Dose and Method of Administration).

Craniosynostosis

In Strensiq clinical studies, adverse events of craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis have been reported in HPP 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 HPP 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 HPP 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 infantile-onset HPP patients below 5 years of age.

Ectopic calcification

Patients with HPP are at increased risk for developing ectopic calcifications.

Ophthalmology examinations and renal ultrasounds are recommended at baseline and periodically during treatment with Strensiq to monitor for signs and symptoms of ophthalmic and renal ectopic calcifications and for changes in vision or renal function.

In clinical trials, events of ectopic calcification including opthalmic (corneal and conjunctival) calcification and nephrocalcinosis have been reported to be at least possibly related to Strensiq. There was insufficient information to determine whether or not the reported events were consistent with the disease or due to Strensiq. No visual changes or changes in renal function were reported resulting from the occurrence of ectopic calcifications.

Serum Parathyroid Hormone and Calcium

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

Disproportionate Weight Gain

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

Use in Hepatic Impairment

Safety and efficacy of Strensiq have not been studied in patients with hepatic impairment.

Use in Renal Impairment

Safety and efficacy of Strensiq have not been studied in patients with renal impairment.

Use in the Elderly

Safety and efficacy of Strensiq in patients older than 65 years have not been established. Therefore, there is no information available to determine whether patients aged 65 years and over respond differently from younger patients.

Paediatric Use

The safety and efficacy of Strensiq have been studied in paediatric patients aged between 0 -18 years. The posology of Strensiq is based on body weight.

Effects on Laboratory Tests

Serum Alkaline Phosphatase

High serum ALP measurements detected through clinical laboratory testing are expected in patients receiving Strensiq and reflect circulating concentrations of asfotase alfa *rch*.

Do not rely on serum ALP measurements for clinical decision making in patients treated with Strensiq.

Laboratory Tests Utilizing Alkaline Phosphatase as a Detection Reagent

Alkaline Phosphatase (ALP) is used as the detection reagent in many routine laboratory assays. Studies have shown that there may be analytical interference between asfotase alfa and laboratory tests that utilize an alkaline phosphatase (ALP)-conjugated test system, rendering potentially erroneous test results in patients treated with Strensiq. ALP-conjugated test systems are utilized to measure substances such as hormones, bacterial antigens and antibodies. Therefore, it is recommended that laboratory assays which do not have ALP-conjugate technology be used when testing samples from patients who are receiving Strensiq.

To avoid erroneous test results for patients treated with Strensiq, inform laboratory personnel that the patient is being treated with Strensiq and discuss the use of a testing platform which does not utilize an ALP-conjugated test system.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with asfotase alfa *rch*. Based on its structure and pharmacokinetics, asfotase alfa *rch* is an unlikely candidate for Cytochrome P450 mediated interactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No adverse effects on fertility were observed in male and female rats given intravenous doses of asfotase alfa *rch* at ≤ 50 mg/kg/day, yielding exposures to asfotase alfa *rch* (based on plasma AUC) up to 19 times higher than that in patients at the recommended human dose of 2 mg/kg SC three times weekly.

Use in Pregnancy – Category C

There are no available data on Strensiq use in pregnant women. Pregnant and lactating women were excluded from Strensiq clinical trials. Strensiq is not recommended during pregnancy, and in women of childbearing potential not using contraception. Patients should be advised to inform their physician if they become pregnant.

Animal studies are insufficient to conclude that asfotase alfa *rch* has no effects on the foetal skeleton. In embryofoetal development studies, no adverse effects were observed in pregnant rats and rabbits that received intravenous doses of asfotase alfa *rch* during organogenesis at doses up to 50 mg/kg/day. These doses resulted in exposures (based on plasma AUC) 18 and 50 times, respectively, the estimated clinical AUC at the recommended human dose of 2 mg/kg SC three times weekly. However, the production of antibodies against asfotase alfa *rch* in rabbits may have affected the detection of reproductive toxicity.

Use in Lactation

There is insufficient information on the excretion of asfotase alfa *rch* in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should not be commenced whilst on treatment with Strensiq.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the Safety Profile

The data described below reflect exposure to Strensiq in 112 patients with perinatal/infantile- (n=89), juvenile-onset (n=22) and adult-onset (n=1) HPP (age at enrolment from 1 day to 66.5 years) treated with Strensiq, most for more than 2 years (range from 1 day to 391.9 weeks [7.5 years]): a majority of patients (69) received at least 120 weeks (2.3 years) of treatment of which 44 patients received 240 weeks (4.6 years) or more of treatment.

The most common adverse reactions were injection site reactions (74%). The majority of these reactions resolved within a week. One patient withdrew from the trial due to an injection site hypersensitivity.

Other common adverse reactions included lipodystrophy, ectopic calcifications and hypersensitivity reactions.

The frequency of injection site reactions, lipodystrophy and ectopic calcification were higher in patients with juvenile-onset HPP as compared to perinatal/infantile-onset HPP patients and was likely due to the increased dosing frequency in older patients.

Table 1 gives the adverse events observed from clinical trials.

Table 1: Adverse Events Reported in at Least 10% of HPP Patients Enrolled in Clinical Trials

MedDRA System Organ Class	Adverse Event[a] (Preferred Term level)	All Patients N=112 n (%)
General disorders and administration site conditions	Injection site reactions (ISRs)[b]	83 (74)
Immune system disorders	Hypersensitivity reactions[c]	22 (20)
Infections and infestations	Upper respiratory tract infection	41 (36.6)
	Nasopharyngitis	30 (26.8)
	Gastroenteritis	27 (24.1)
	Pneumonia	25 (22.3)
	Respiratory tract infection	17 (15.2)
	Otitis media	16 (14.3)
	Conjunctivitis	15 (13.4)
	Ear infection	15 (13.4)
	Bronchitis	13 (11.6)
	Influenza	13 (11.6)
	Rhinitis	13 (11.6)
	Viral infection	12 (10.7)

Gastrointestinal disorders	Tooth loss	49 (43.8)
	Vomiting	45 (40.2)
	Diarrhoea	28 (25.0)
	Constipation	25 (22.3)
	Dental caries	14 (12.5)
	Gastrooesophageal reflux disease	14 (12.5)
Injury, poisoning and procedural complications	Procedural pain	20 (17.9)
	Contusion	18 (16.1)
	Fall	17 (15.2)
Respiratory, thoracic and mediastinal disorders	Cough	29 (25.9)
	Oropharyngeal pain	12 (10.7)
Skin and subcutaneous tissue disorders	Rash	16 (14.3)
	Dermatitis diaper	12 (10.7)
Musculoskeletal and connective tissue disorders	Pain in extremity	33 (29.5)
	Arthralgia	25 (22.3)
	Back pain	14 (12.5)
Nervous system disorders	Headache	29 (25.9)
Congenital, familial and genetic disorders	Craniosynostosis	26 (23.2)
Blood and lymphatic system disorders	Anaemia	12 (10.7)
Miscellaneous [d]	Ectopic calcifications [e]	44 (39)

[a]All adverse events, regardless of causality assessment, are included
[b]Preferred terms considered as ISRs are presented in Description of select adverse reactions section below
[c]Preferred terms considered as hypersensitivity reactions are presented in Description of select adverse reactions section below.
[d]The terms pooled under 'Ectopic calcifications' (see footnote d) span multiple SOC, including 'Eye disorders', 'Renal and urinary disorders', 'Musculoskeletal and connective tissue disorders' and 'Reproductive system and breast disorders'.
[e]Preferred terms considered as ectopic calcifications (listed in order of decreasing frequency), include nephrocalcinosis, conjunctival deposit, deposit eye, corneal deposits, optic disc drusen, chondrocalcinosis pyrophosphate, hydronephrosis and breast calcification.

Less common adverse reactions

Adverse reactions that occurred at rates less than 10% included;

- Hypocalcaemia
- Renal stones
- Chronic hepatitis
- Decreased vitamin B6
- Skin discolouration
- Skin hyperpigmentation

Description of selected adverse reactions

Injection Site Reactions (ISRs)

ISRs (including injection site atrophy, abscess, erythema, discoloration, pain, pruritus, macule, swelling, contusion, bruising, lipodystrophy (lipoatrophy or lipohypertrophy), induration, reaction, nodule, rash, papule, haematoma, inflammation, urticaria, calcification, warmth, haemorrhage, cellulitis, scar, mass, extravasation, exfoliation and

vesicles) are the most common adverse reactions, observed in approximately 74% of the patients in the clinical studies.

Hypersensitivity

Hypersensitivity reactions (including irritability, pyrexia, rash, pruritis, chills, erythema, nausea, vomiting, flushing, oral hypoesthesia, headache, tachycardia and cough) are very common adverse reactions, observed in approximately 22/112 (19.6%) of the patients in the clinical studies. 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

As with all therapeutic proteins, there is potential for immunogenicity. Among 109 HPP patients enrolled in the clinical trials, 97/109 (89.0%) tested positive for anti-drug antibodies at some time point after receiving 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. Formation of anti-drug antibodies resulted in reduced systemic exposure of asfotase alfa *rch*. In clinical trials, the development of antibodies has not been shown to affect clinical efficacy or safety.

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

Cases from the post-approval setting suggest that development of inhibitory antibodies may be associated with a decreased clinical response.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The maximum dose of Strensiq used in clinical trials is 28mg/kg/week. No dose-related toxicity or change in the safety profile has been observed in clinical studies to date; therefore no overdose level has been determined.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Hypophosphatasia (HPP) is a rare, serious, and potentially fatal, genetic disorder caused by loss-of-function mutation(s) in the gene encoding TNSALP. In patients with HPP, a deficiency in TNSALP enzymatic activity leads to elevations in several TNSALP substrates, including inorganic pyrophosphate (PPi). Elevated extracellular levels of PPi block hydroxyapatite crystal growth which inhibits bone mineralisation and causes accumulation of unmineralised bone matrix which manifests as rickets and bone deformations in infants and children and as osteomalacia (softening of bones) once growth plates close, along with muscle weakness. Replacement of the TNSALP enzyme upon Strensiq treatment reduces the enzyme substrate levels.

Asfotase alfa *rch*, a human recombinant TNSALP-Fc-deca-aspartate fusion protein with enzymatic activity, promotes mineralisation of the skeleton in patients with HPP.

Pharmacodynamics

Perinatal/infantile-and juvenile-onset HPP patients treated with Strensiq had reductions in plasma TNSALP substrates, PPi and pyridoxal 5'-phosphate (PLP) within 6 to 12 weeks of treatment. Reductions in plasma PPi and PLP levels did not correlate with clinical outcomes. In adult patients with paediatric-onset HPP, the pharmacodynamics of Strensiq was consistent with those observed in paediatric patients with perinatal/infantile-onset or juvenile-onset HPP.

Bone biopsy data from perinatal/infantile-onset and juvenile-onset HPP patients treated with Strensiq demonstrated decreases in osteoid volume and thickness indicating improved bone mineralization.

Clinical Trials

Due to HPP being an ultra-rare (orphan) disease, only limited, Phase II data have been provided in support of the safety and efficacy of Strensiq in the treatment of HPP.

Four studies were conducted in the clinical development program for Strensiq, in which a total of 111 patients with paediatric-onset HPP were enrolled. Of these 111 patients, 89 had perinatal- or infantile-onset HPP, while 22 had juvenile-onset HPP. In Studies ENB-002-08/ENB-003-08 and ENB-010-10, eligible patients had perinatal- or infantile-onset HPP and were ≤ 3 or ≤ 5 years of age at enrolment, respectively. In Study ENB-006-09/ENB-008-10, eligible patients were required to have perinatal- or infantile- or juvenile-onset disease and be aged between 5 and 12 years at enrolment, while in Study ENB-009-10, eligible patients had perinatal- or infantile- or juvenile-onset and were aged between 13 and 65 years at enrolment. Patient demographics in HPP clinical trials are summarised in Table 2 below.

Table 2: HPP Clinical trials

Study	Trial design	No of patients (n)	Age range
ENB-002-08	Multicentre, open-label, single group assignment, safety/efficacy phase II study in infants and young children (*perinatal-/infantile onset*)	11	3 weeks to 39.5 months
ENB-003-08 (extension study)		10	
ENB-010-10	Multicentre, open-label, single group assignment, safety/efficacy, PK phase II study in infants and children (*perinatal-/infantile onset*)	69	1 day to 5 years
ENB-006-09	Multicentre, open-label, dose comparison, parallel assignment, historical control, safety/efficacy, PK, PD phase II study in infants and early adolescents (*perinatal-/infantile and juvenile onset*)	13	5 to 12 years
ENB-008-10 (extension study)		12	
ENB-009-10	Randomized, multicentre, open-label, dose-ranging, concurrent control, safety/efficacy, PK phase II study in adolescents and adults (*perinatal-infantile-, juvenile- and adult onset*)	19	13 to 66 years

Baseline characteristics of patients with paediatric-onset HPP evaluated in clinical trials included low ALP and one or more of the following; elevated TNSALP biochemical substrates (PPi and PLP), abnormal bone structure (elevated osteoid indices, reduced bone mineral content, skeletal deformities of rickets such as bowed legs, abnormally shaped chest, below normal Z-score for height) or impaired physical function (gross motor weakness, developmental delay, impaired walking, inability to perform activities of daily living). At baseline, patients less than 5 years of age presented with additional morbidities including nephrocalcinosis, seizures, respiratory compromise (including respiratory failure requiring support) and gross motor delays. In Study ENB-002-08/ENB-003-08, most patients (9/11, 81.8%) presented with significant gross motor delays on the BSID-III (Bayley Scales of Infant and Toddler Development, Third Edition) e.g. gross motor scaled scores of 1, which is 3 SDs below the mean SD for healthy age-matched peers. In Study ENB-009-10, 18/19 (94.7%) patients experienced fractures and 18 patients had bone pain severe enough to limit activity.

Subcutaneous doses of 6 mg/kg/week of Strensiq were administered 3 times a week or 6 times a week. After completion of the initial 24-week treatment period in ENB-002-08 and ENB-006-09, most patients continued to receive Strensiq by enrolling into an extension study.

<u>Study ENB-002-08/ENB-003-08</u>

Study ENB-002-08/ENB-003-08 was a 24 week prospective single arm trial in 11 patients aged 3 weeks to 39.5 months, with severe perinatal/infantile-onset HPP; 7/11 (64%) were female and 10/11 (91%) were white. Severe perinatal/infantile-onset HPP was defined as biochemical, medical history and radiographic evidence of HPP as well

as the presence of any of the following: respiratory compromise, rachitic chest deformity, vitamin B6-dependent seizures, and/or failure to thrive. Ten of 11 patients completed the 24-week trial and continued treatment in the extension phase. Nine patients have been treated with Strensiq for at least 5 years (60 months) and 4 patients have been treated for more than 7 years (84 months).

Study ENB-010-10

Study ENB-010-10 was prospective open-label study in 69 patients, aged 1 day to 5 years with perinatal/ infantile-onset HPP; 54/69 (78%) were white. 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).

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

Study ENB-006-09/ENB-008-10 was a prospective open-label 24 week trial that enrolled 13 patients that included 5 perinatal/ infantile-onset HPP patients and 8 juvenile-onset HPP patients. Twelve of the 13 patients entered the extension study and were treated for at least 6 years (72 months).

Study ENB-009-10

Study ENB-009-10 was an open-label, randomised study that enrolled 19 patients. Patients were randomly assigned to 1 of 2 Strensiq treatment groups (either 0.3 mg/kg/day or 0.5 mg/kg/day) or to the prospective control group for the 24-week primary treatment period. All patients received Strensiq treatment (0.5 mg/kg/day) in the extended treatment period. After 48 weeks all patients were adjusted to the recommended dose 1.0 mg/kg/day. Fourteen patients completed and 5 discontinued the study. At study completion, the median treatment period was 60 months (range, 24 to 68 months). Four patients had perinatal/infantile-onset HPP, 14 patients had juvenile-onset HPP, and 1 patient had adult-onset HPP. Age was 13 to 66 years at inclusion and was between 17 and 72 years at study completion.

Study Results

Perinatal/Infantile-onset HPP

Skeletal Manifestations

Radiographs from 81 Strensiq-treated perinatal/infantile-onset HPP patients, including 77 patients in ENB-002-08/ENB-003-08 & ENB-010-10, and 4 patients in ENB-006-09/ENB-008-10, were examined to assess HPP-related rickets using the 7-point Radiographic Global Impression of Change (RGI-C) scale. Patients with a minimum RGI-C score of +2 were defined as “responders”. Radiologic improvements could be seen by Week 24; at last assessment, 63/81 [78%] treated patients were rated as RGI-C responders. No comparative data were available from historical controls. The mean time interval between the baseline and last RGI-C assessment was 35.7 months (range was 2.5 months to 89.4 months).

Radiographs were also scored using the 10-grade Rickets Severity Scale (RSS), which can be used to quantify the severity of rickets in the wrists and knees of these patients based on the degree of metaphyseal fraying and cupping and the proportion of growth plate affected. A score of 10 represents severe rickets, while a score of 0 represents an

absence of rickets. Change in RSS scores were also statistically significant, with progressive improvements (at Week 24, median change in RSS score was -1.5, and at last overall assessment, the median change was -3.0).

Growth

Height and weight measurements (as measured by Z-scores) were available post-treatment for 82 perinatal/infantile-onset HPP patients, including 78 patients enrolled in Studies ENB-002-08/ENB-003-08 & ENB-010-10, and 4 patients enrolled in ENB-006-09/ENB-008-10 (Table 3).

Table 3: Perinatal/Infantile-Onset Height and Weight Measurements as Measured by Z-Score

	Height Z-score				**Weight Z-score**			
	Baseline		**Last Assessment**		**Baseline**		**Last Assessment**	
	Mean	**Min, Max**	**Mean**	**Min, Max**	**Mean**	**Min, Max**	**Mean**	**Min, Max**
ENB-002-08/ENB-003-08 & ENB-010-10 (N = 78) [a]	-3.3	-10.1, 0.9	-2.9	-12.3, 0.7	-3.2	-23.8, 0	-2.3	-19.9, 1.4
ENB-006-09/ENB-008-10 (N = 4)[b]	-2.6	-6.6, -0.7	-1.4	-5.4, 0.4	-2.5	-8.2, -1.0	-1.6	-5.4, 0.6

[a] The mean time interval between baseline and last assessment was 33.8 months (range was 0.7 month to 89.4 months).
[b] The mean time between baseline and last assessment was 77.6 months (range was 76.6 months to 79.0 months).

Survival and Ventilation-Free Survival

Survival and invasive ventilation-free survival were compared in Strensiq-treated patients with severe perinatal- or infantile-onset HPP (ENB-002-08/ENB/003-08 and ENB-010-10) with a historical cohort of untreated patients with similar clinical characteristics (ENB-011-10), all of whom had a history of rachitic chest deformity, vitamin B6-dependent seizures, and/or failure to thrive (Table 4 and Figure 1).

Table 4: Survival and Invasive Ventilation-Free Survival in Strensiq-treated versus Historical Control Patients with Perinatal/Infantile-Onset HPP

	Strensiq-Treated	**Historical Control**
Survival	n = 78	n = 48
Alive at Point of Last Contact (%)	69 (88%)	13 (27%)
Hazard Ratio (Strensiq/Historical Control), 95% Confidence Interval*	0.174 (0.072, 0.421)	
Kaplan-Meier Estimate and Alive at Age 1 Year (Week 48) (%)	94	42

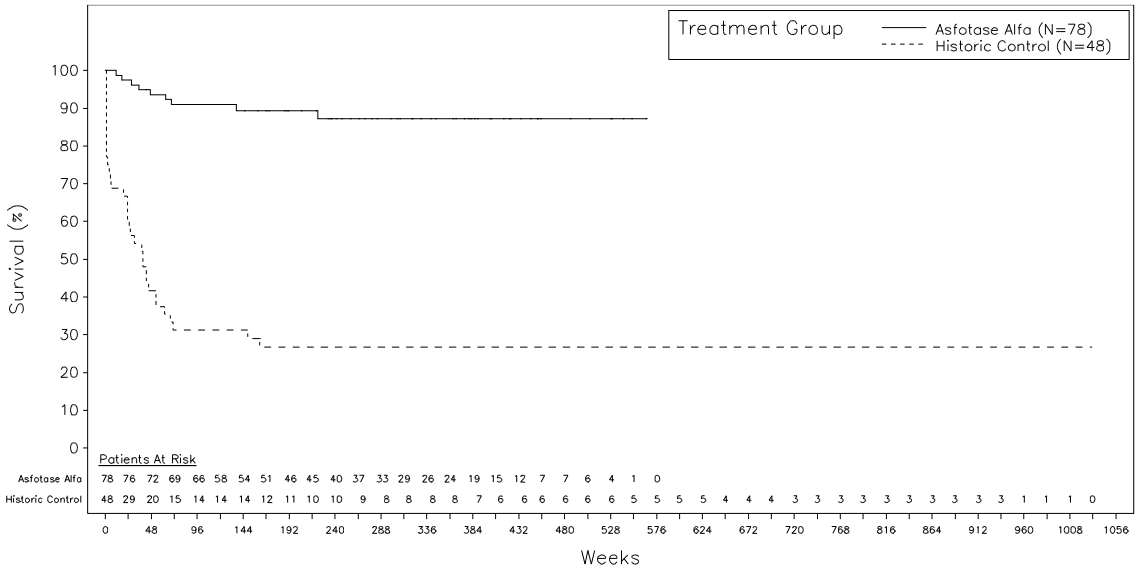
	Strensiq-Treated	Historical Control
Invasive Ventilation-Free Survival**	n = 62	n =48
Alive and Not on Ventilation at Point of Last Contact (%)	51 (82%)	12 (25%)
Hazard Ratio (Strensiq/Historical Control), 95% Confidence Interval*	0.236 (0.103, 0.540)	
Kaplan-Meier Estimate of Alive and Not on Ventilation at Age 1 Year (Week 48) (%)	92	31

* Adjusted for year of diagnosis.

**Alive and not initiating invasive ventilation after start of Strensiq treatment. Strensiq-treated-patients on invasive ventilation at baseline were excluded from this analysis.

Overall survival was improved in the cohort of treated patients with severe perinatal- or infantile-onset HPP, compared to the matched historical control group, with 69/78 (88%) treated patients vs. 13/48 (27%) historical controls alive at last contact. In patients who required any form of respiratory support, 23/29 (79%) of the treated patients survived through their last assessment (median age at last assessment was 3.9 years), versus 1 of 20 (5%) of historical controls.

Figure 1: Overall Survival in Strensiq-Treated versus Historical Control Patients with Severe Perinatal/Infantile-Onset HPP



Ventilation support

The natural history of untreated infant HPP patients suggests higher mortality if ventilation is required. 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. 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

Juvenile-onset HPP

Skeletal Manifestations

In study ENB-006-09/ENB-008-10, radiographs from 8 Strensiq-treated patients and 32 historical controls were compared to assess HPP-related rickets using the 7-point RGI-C (Radiographic Global Impression of Change) scale. Patients who achieved a RGI-C score of 2 or higher (corresponding to substantial healing of rickets) were classified as being responders to treatment. All 8 treated patients were rated as responders by Month 54 of treatment. The mean duration between the baseline and last RGI-C assessments for control patients was 56 months (range was 8 to 95 months). At last assessment, 2/32 (6%) of control patients were rated as responders.

Gait/Mobility

Gait was assessed using a modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale) in 8 Strensiq-treated patients at 6 month intervals out to 36 months. Step length improved by at least 1 point in either foot in 6/8 patients compared to 1/6 (17%) control patients. Mobility was also assessed using the 6 Minute Walk Test (6MWT) in 7 of the 8 patients. At last assessment, all 7 patients had an improvement in distance walked of at least the minimal clinically important difference. The mean increase from baseline for distance walked is 222.4 meters (range from 81 to 297 meters). Mean walking distance reached the normal range after 6 months of treatment and improvements were sustained over 6 years.

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.

At baseline, the mineralisation indices; osteoid thickness, osteoid volume per bone volume and mineralisation lag time were all elevated, relative to a normative sample of healthy individuals, which was consistent with osteomalacia. At Week 24, all 3 parameters had declined significantly from their pre-treatment levels, associated with improved bone mineralisation. The results 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 Strensiq are presented in Table 5 below.

Table 5: Baseline and week 24 in bone histomorphology on trans-iliac crest bone biopsy in paediatric-onset HPP patients (infantile and juvenile-onset subgroups) aged 5-12 years

		Baseline	**Week 24**
Osteoid thickness	mean (SD)	12.8 (3.5) µm	9.5 (5.1) µm
Osteoid volume / bone volume	mean (SD)	11.8 (5.9) %	8.6 (7.2) %
Mineralisation lag time	mean (SD)	93 (70) days	119 (225) days

Growth

Height, weight and head circumference were plotted on growth charts (series of percentile curves that illustrate distribution) available from the Centres 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 HPP.

For those patients who received Strensiq: 9/13 patients displayed persistent apparent catch-up height-gain as shown by movement over time to a higher percentile on CDC growth charts. Three of the 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 section 4.4 – Special Warnings and Precautions for Use; Serum Parathyroid Hormone and Calcium).

Adolescent and Adult Patients with HPP

Bone Biopsy

A histomorphometric assessment (transiliac crest bone biopsy) was conducted in ENB-009-10. Patients underwent biopsy of the trans-iliac bone crest either as part of a control group or before and after exposure to Strensiq and results are presented in Table 6 below.

Table 6: Baseline and Week 24/Week 48* Mineralisation lag-time on trans-iliac crest bone biopsy in HPP patients (adolescent and adult patients)

	Mean (SD) mineralisation lag-time (days)	
	Baseline	**Week 24/Week 48***
Control group, standard of care (5 evaluable patients)	226 (248)	304 (211)
0.3 mg/kg/day asfotase alfa rch group (4 evaluable patients)	1236 (1468)	328 (200)
0.5 mg/kg/day asfotase alfa rch group (5 evaluable patients)	257 (146)	130 (142)

*Week 24 for Control group and Week 48 for the Strensiq groups.

Physical Function and Growth

Physical function was evaluated in ENB-009-10 using the 6 minute walk test (ambulation). At Week 24, change from baseline in distance walked in 6 minutes (6MWT) was 35.0 (-2, 182) m for the combined treatment group and -6.5 (-46, 113) m for the control group. The difference between treated and untreated patients did not achieve statistical significance due to patient heterogeneity, low Strensiq dose and/or the small sample size of the study. During the extended treatment period, most patients had sustained or increased improvements.

There was no improvement in height in the overall study population in Study ENB-009-10; however, this was expected given that 6/19 of the patients were adolescents at the time of enrolment.

5.2 PHARMACOKINETIC PROPERTIES

Based on data in 38 HPP patients the pharmacokinetics of asfotase alfa *rch* exhibited dose proportionality across the dose range of 0.3 mg/kg to 3 mg/kg, administered three times per week, and appeared to be time-independent. Steady state exposure was achieved as early as three weeks after the administration of the first dose. The elimination half-life following subcutaneous administration was approximately 5 days. In adult patients with paediatric-onset HPP, the pharmacokinetics of asfotase alfa *rch* at doses of 0.5, 2 and 3 mg/kg administered three times per week was consistent with those observed in paediatric patients with paediatric-onset HPP, and thus supported the approved dose of 6 mg/kg per week in treating adult patients with paediatric-onset HPP.

Table 7 summarises the pharmacokinetic parameters following multiple doses in 20 HPP patients after subcutaneous administration of Strensiq at 2 mg/kg three times per week in Study ENB-010-10 (age of less than or equal to 5 years) and Study ENB-006-08/ENB-008-10 (age of greater than 5 to 12 years), indicating the pharmacokinetics were similar between patients in the two age groups.

Table 7: Summary of Pharmacokinetic Parameters Following Multiple Subcutaneous Administration of Strensiq 2 mg/kg Three Times per Week

	ENB-010-10	ENB-006-09/ENB-008-10
N	14	6

Age (year)	3.4 ± 2.1	8.6 ± 2.2
	(0.2, 6.2)	(6.1, 12.6)
Weight at baseline (kg)	11.2 ± 5.0	21.2 ± 7.9
	(2.9, 17.1)	(11.4, 35.4)
t_{last} (h)	48.1 ± 0.1 (47.9, 48.3)	48.0 ± 0.1 (48.0, 48.1)
t_{max} (h)	14.9 ± 10.4 (0, 32.2)	20.8 ± 10.0 (11.9, 32.2)
Cmax (ng/mL)	1794 ± 690 (856, 3510)	2108 ± 788 (905, 3390)
AUCt (h*ng/mL)	66042 ± 25758	89877 ± 33248
	(27770, 119122)	(37364, 142265)
Accumulation Ratio[a]	1.5	3.9

[a]Ratio values reflect the fold increase of AUCt from Week 1 based on mean AUCt, values.
Data are presented as mean ± standard deviation (range). Study ENB-006-08/ENB-008-10 includes patients with perinatal/infantile-or juvenile-onset of disease. tlast, time of last concentration; tmax, time of maximal concentration; Cmax, maximal concentration; AUCt, area under the concentration-time curves over a dosing interval of 48 hours.

Based on the results of population pharmacokinetic analysis, body weight was identified to affect asfotase alfa *rch* clearance and volume of distribution parameters. It is expected that pharmacokinetic exposures will increase with body weight. The impact of immunogenicity on asfotase alfa *rch* pharmacokinetic varied over time due to the time varying nature of immunogenicity and overall was estimated to decrease pharmacokinetic exposures by less than 20%.

Formation of anti-drug antibodies resulted in reduced systemic exposure of asfotase alfa *rch.*

The extrinsic factors affecting asfotase alfa *rch* pharmacokinetic exposures were formulation specific activity and total sialic acid content.

Absorption

Following weekly SC administrations of Strensiq, the observed median T_{max} ranged from 1 to 2 days and the absolute bioavailability ranged from 45.8-98.4%. Following once weekly administration of Strensiq 3 mg/kg IV bolus on Week 1 followed by 2 mg/kg SC on Weeks 2, 3 and 4, the Week 4 mean ± SD observed C_{max} and AUC_t parameters were 1020 ± 326 U/L and 284,926 ± 79,652 U*h/L, respectively.

Distribution

Based on population PK analysis, the estimated central and peripheral volumes of distribution (mean) for a patient with body weight 70kg were 5.66 L (95% CI: 2.76, 11.6) and 44.8 L (95% CI: 33.2, 60.5), respectively. These results indicated that asfotase alfa *rch* was initially distributed primarily in the intra-vascular space and then distributed to the extra-vascular space, reflecting its ability to partition into tissues, likely including skeletal tissue.

Metabolism

In vitro or *in vivo* metabolism studies are not considered relevant since the expected metabolic pathway is the normal catabolic degradation into small peptides and individual amino acids.

Excretion

The central and peripheral clearance estimates for a patient with body weight 70kg (and 95% CI) were 15.8 (13.2, 18.9) L/day and 51.99 (44.0, 61.2) L/day respectively. The average elimination half-life of asfotase alfa *rch* was 2.28 ± 0.58 days with a range of 1.06 to 3.62 days.

Special Populations

Based on the population PK analysis, age and sex were not found to be significant covariates.

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.

Significant PK-PD relationships were demonstrated based on the efficacy biomarker data and clinical endpoints in patients with paediatric-onset HPP, across the range of perinatal/infantile and juvenile-onset cohorts. These relationships supported the recommendation of the 6 mg/kg/week dose, administered as either 2 mg/kg 3-times weekly or 1 mg/kg 6-times weekly.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted to assess the genotoxic potential of asfotase alfa *rch.*

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of asfotase alfa *rch.*

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sodium chloride
dibasic sodium phosphate heptahydrate
monobasic sodium phosphate monohydrate
water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Do not use beyond the expiration date (EXP) stamped on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Strensiq vials must be stored in a refrigerator (2° to 8° C, Do not freeze) in the original packaging in order to protect from light.

Out of refrigeration, the product should be kept at room temperature and administered within 3 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Strensiq is supplied as packs of 12 single-use glass vials as follows;

Concentration	Strength	Fill volume
40 mg/mL	12 mg/vial	0.3 mL
	18 mg/vial	0.45 mL
	28 mg/vial	0.7 mL
	40 mg/vial	1.0 mL
100 mg/mL	80 mg/vial	0.8 mL

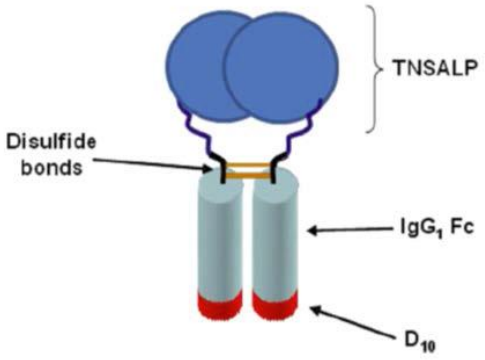
Note: not all presentations above may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any unused portion left in the vial, as the product contains no preservatives. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

CAS registry number: 1174277-80-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Alexion Pharmaceuticals Australasia Pty Ltd
Suite 401. Level 4. Building A
20 Rodborough Rd
Frenchs Forest NSW 2086

Medical enquiries: 1800 788 189

9 DATE OF FIRST APPROVAL

14 January 2016

10 DATE OF REVISION

12 October 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
3	Minor editorial changes to update Pharmaceutical form as per approved Module 3 information