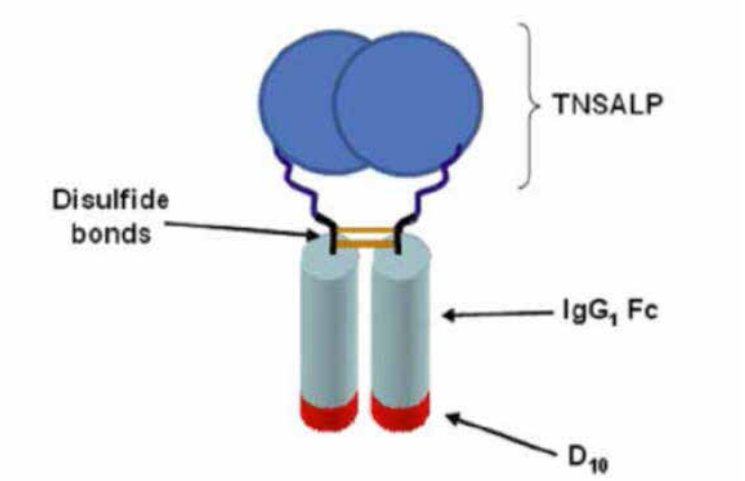
STRENSIQ®

NAME OF THE MEDICINE

STRENSIQ®
Asfotase alfa *rch* solution for injection



(CAS registry number: 219685-50-4).

DESCRIPTION

STRENSIQ is supplied as a single-use vial containing 40 or 100 mg/mL of asfotase alfa *rch* with the following excipients sodium chloride, sodium phosphate - dibasic heptahydrate, sodium phosphate - monobasic monohydrate and Water for Injections.

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.

PHARMACOLOGY

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, deficiency in TNSALP enzymatic activity leads to elevated concentrations of the TNSALP substrates, including inorganic pyrophosphate (PPi). Elevated extracellular levels of PPi block hydroxyapatite crystal growth which inhibits bone mineralization and causes accumulation of unmineralized 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.

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 asfotase alfa, *rch* 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.

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

Pharmacokinetics

The pharmacokinetics of asfotase alfa *rch* exhibited dose proportionality across the dose range of 0.3 mg/kg to 3 mg/kg and appeared to be time-independent. 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 asfotase alfa *rch*, 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 asfotase alfa, *rch* 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.

Pharmacokinetics in 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 asfotase alfa *rch* 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.

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 asfotase alfa, *rch* in the treatment of HPP.

Patients were enrolled in 3 pivotal prospective studies and their extensions and a retrospective natural history study (ENB-011-010) was conducted to provide an untreated historical cohort for comparisons of overall and invasive ventilator-free survival. Additionally, a supportive study enrolled 19 patients aged 13-66 years, 16 of these patients had paediatric-onset HPP.

Patient demographics in HPP clinical trials are summarised in Table 1 below.

Table 1: 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 (*infantile onset*)	11	6 months to 3 years
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 (*infantile onset*)	28	0 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 (*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 (*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 1, 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 4, 18 (94.7%) patients experienced fractures and 18 (94.7%) patients had bone pain severe enough to limit activity.

Subcutaneous doses of 6 mg/kg/week of asfotase alfa *rch* 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 asfotase alfa *rch* by enrolling into an extension study. The median duration of treatment was approximately 206 weeks (min, max: 0.1, 260.9) in ENB-002-08/ENB-003-08, 56 weeks (min, max: 0.4, 171.3) in ENB-010-10 and 182 weeks (min, max: 4.4, 207.9) in ENB-006-09/ENB-008-10.

In all pivotal efficacy studies, the primary endpoint was change in Radiographic Global Impression of Change (RGI-C) scores at 24 weeks. The RGI-C scale provides a radiological evaluation of bone structure for findings that are associated with the pathophysiology of HPP. Trained radiologists evaluated pre- and post-baseline x-rays of wrists and knees of patients for the following signs: apparent physeal widening, metaphyseal flaring, irregularity of provisional zone of calcification, metaphyseal radiolucencies, metadiaphyseal sclerosis, osteopenia, 'popcorn' calcification in metadiaphysis, demineralization of distal metaphysis, transverse subphyseal band of lucency and tongues of radiolucency. X-ray changes from baseline were rated using the RGI-C 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.

Study results

Study ENB-002-08/ENB-003-08

Study ENB-002-08/ENB-003-08 was an open-label, non-randomised, non-controlled study that enrolled 11 patients (9 patients are on-going) aged < 36 months. Onset of HPP was under 6 months in all patients.

Seven of the 11 patients in the full analysis set achieved RGI-C scores of +2 at Week 24 compared to baseline radiographs. Five of the 11 patients 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-006-09/ENB-008-10

Study ENB-006-09/ENB-008-10 was an open-label, non-randomised study that enrolled 13 patients aged 5-12 years of age (12 patients are on-going). Five patients presented with

HPP before 6 months age and 8 patients presented after 6 months age. The study employed historical controls from the same centre as patients who received asfotase alfa, *rch* and who had been subject to a similar protocol of clinical management.

The effects of asfotase alfa, rch on x-ray appearance
Patients who received asfotase alfa, *rch* moved to RGI-C 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. 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 asfotase alfa, *rch* are presented in Table 2 below.

Table 2: 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 asfotase alfa, *rch*: 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 PRECAUTIONS, Serum Parathyroid Hormone and Calcium).

Study ENB-009-10

Study ENB-009-10 was an open-label, non-randomised study that enrolled 19 patients (18 patients are on-going) aged from 13 to 66 years. Onset of HPP 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.

Bone biopsy
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, *rch*: and results are presented in Table 3 below.

Table 3: 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 asfotase alfa, *rch* groups.

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

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 (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

INDICATIONS

STRENSIQ (asfotase alfa *rch*) is indicated as enzyme replacement therapy in patients with

paediatric-onset hypophosphatasia.

CONTRAINDICATIONS

Asfotase alfa, *rch* 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.

PRECAUTIONS

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 asfotase alfa, *rch* in the treatment of HPP.

Hypersensitivity

Hypersensitivity reactions have been reported in asfotase alfa, *rch* -treated patients. In clinical trials, 1 out of 99 patients (1%) treated with asfotase alfa, *rch* experienced signs and symptoms consistent with anaphylaxis, including difficulty breathing, nausea, periorbital oedema and dizziness. In this patient, the reaction occurred approximately 1 minute after asfotase alfa, *rch* injection in the setting of 3.5 years of ongoing asfotase alfa, *rch* treatment and resolved without medical treatment. Other hypersensitivity reactions have also been reported in asfotase alfa, *rch* -treated patients; including vomiting, fever, headache, flushing, irritability, chills, skin erythema, rash, pruritus and oral hypoesthesia (see ADVERSE EFFECTS).

Other severe allergic type hypersensitivity reactions are possible, including urticaria, difficulty breathing and/or cardiovascular collapse. If these reactions occur, immediate discontinuation of asfotase alfa, *rch* 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 following asfotase alfa, *rch* administration.

Injection Reaction

Administration of asfotase alfa, *rch* 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 *Adverse Effects*). 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. One patient treated in clinical trials experienced a severe ISR of injection site discolouration which led to the discontinuation of asfotase alfa, *rch*.

Asfotase alfa, *rch* administration should be interrupted in any patient experiencing severe injection reactions and appropriate medical therapy administered.

Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with asfotase alfa, *rch* in clinical trials. Patients should be advised to follow proper injection technique and to rotate injection sites.

Craniosynostosis

In asfotase alfa, *rch* 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 asfotase alfa, *rch* 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

In asfotase alfa, *rch* clinical studies ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis have been reported in patients with hypophosphatasia. There are insufficient data to establish a causal relationship between exposure to asfotase alfa, *rch* 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 concentrations may increase in HPP patients administered asfotase alfa, *rch*, 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, *rch*. Supplements of calcium and oral vitamin D may be required.

Disproportionate weight gain

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

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 asfotase alfa, *rch* use in pregnant women. Pregnant and lactating women were excluded from asfotase alfa, *rch* clinical trials. Asfotase alfa, *rch* 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 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 asfotase alfa, *rch*.

Paediatric Use

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

Use in the Elderly

Safety and efficacy of asfotase alfa, *rch* 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.

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*.

Effects on Laboratory Tests

Asfotase alfa, *rch* contains a catalytic domain of tissue non-specific alkaline phosphatase. Administration of asfotase alfa, *rch* 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.

Use in Renal Impairment

Safety and efficacy of asfotase alfa, *rch* have not been studied in patients with renal impairment.

Use in Hepatic Impairment

Safety and efficacy of asfotase alfa, *rch* have not been studied in patients with hepatic impairment.

INTERACTIONS WITH OTHER MEDICINES

Drug interaction studies have not been performed with asfotase alfa, *rch*. Based on its structure and pharmacokinetics, asfotase alfa *rch* is an unlikely candidate for Cytochrome P450 mediated interactions.

ADVERSE EFFECTS

Summary of the safety profile

In clinical trials, 71 patients (age 1 day to 66 years) were treated with asfotase alfa, *rch*, of which, 68 had paediatric-onset HPP, with the majority for more than 2 years (range 0.1 to 260.9 weeks). The most common adverse reactions observed were injection site reactions and injection associated reactions. The majority of these reactions were non-serious, and mild to moderate in intensity. Serious adverse reactions of injection associated reactions were reported in 2 patients with no discontinuation of asfotase alfa, *rch* treatment: 1 patient with infantile-onset reported as fever and chills, and in 1 patient with juvenile-onset HPP reported as hypoaesthesia oral, pain in extremity, chills, and headache.

Other common adverse reactions included lipodystrophy (32.4%), ectopic calcifications (17.6%), and hypersensitivity reactions (16.2%).

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.

Tabulated list of adverse reactions

Presented in Table 4 below are the adverse reactions observed from clinical trials following SC injection of asfotase alfa *rch*. Adverse reactions reported as, very common (≥1/10), common (≥1/100 to <1/10) or uncommon (≥1/1,000 to <1/100) are listed by system organ class (SOC) and preferred term. Due to the small patient population in the clinical trials, an adverse reaction reported in 1 patient is considered as common. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse Reactions Reported in HPP clinical trials (patients aged 1 day to 66 years)

MedDRA SOC	Frequency	Adverse reaction
General disorders and administration site conditions	very common	Injection site reactions (ISRs)^ Pyrexia Irritability
	common	Chills
Skin and subcutaneous tissue disorders	very common	Erythema
	common	Lipohypertrophy Cutis laxa Skin discolouration including hypopigmentation Skin disorder (stretched skin)

MedDRA SOC	Frequency	Adverse reaction
Gastrointestinal disorders	common	Hypoaesthesia, oral Nausea
Musculoskeletal and connective tissue disorders	very common	Pain in extremity
	common	Myalgia
Injury, poisoning and procedural complications	very common	Contusion
	common	Scar
Vascular disorders	common	Hot flush
Blood and lymphatic system disorders	common	Increased tendency to bruise
Infections and infestations	common	Injection site cellulitis
Nervous system disorders	very common	Headache

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

Less common adverse reactions

Adverse reactions that occurred at rates less than 1% included;

- Hypocalcaemia
- Renal stones
- Chronic hepatitis
- Decreased vitamin B6

Description of selected adverse reactions

Injection site reactions (ISRs)

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

Immunogenicity

There is potential for immunogenicity. Among 69 HPP patients enrolled in the clinical trials, 56 (81.2%) tested positive for anti-drug antibodies at some time point after receiving asfotase alfa, *rch* 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. Formation of anti-drug antibodies resulted in reduced

systemic exposure of asfotase alfa *rch.* The development of antibodies has not been shown to affect clinical efficacy of safety.

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, *rch*.

DOSAGE AND ADMINISTRATION

Asfotase alfa, *rch* treatment should be initiated by a physician experienced in the management of patients with metabolic or bone disorders.

Patient Monitoring Program: physicians should enroll consenting patients receiving asfotase alfa, *rch* 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, multiple injections may be administered at different injection sites.

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	100mg	50 mg

60	120mg	60 mg
70	140mg	70 mg
80	160mg	80 mg
90	180mg	90 mg
100	200mg	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.

Asfotase alfa, *rch* should be administered using sterile disposable syringes and injection needles. 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. **Asfotase alfa, *rch* must be administered as subcutaneous injection**.

Injections sites should be rotated and carefully monitored for signs of potential reactions.

Product is for single use in one patient only. Discard any unused portion left in the vial, as the product contains no preservatives.

Special Populations

Patients with renal and hepatic impairment: the safety and efficacy of asfotase alfa, *rch* 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.

OVERDOSAGE

The maximum dose of asfotase alfa *rch* 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).

PRESENTATION AND STORAGE CONDITIONS

STRENSIQ is a clear, colourless to slightly yellow solution for subcutaneous injection. It is supplied in 2 mL single-use glass vials as follows;

Pack sizes	Fill volume	Concentration	Strength
12 vials per pack or 1 vial per pack	0.3 mL	40 mg/mL	12 mg/vial
	0.45 mL		18 mg/vial
	0.7 mL		28 mg/vial
	1.0 mL		40 mg/vial
	0.8 mL	100 mg/mL	80 mg/vial

Note: not all presentations above may be available.

Storage conditions

STRENSIQ vials must be stored in a refrigerator (2 º to 8º 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 1 hour.

Do not use beyond the expiration date (EXP) stamped on the packaging. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF SPONSOR

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

Medical enquiries: 1800 788 189

POISONS SCHEDULE OF THE MEDICINE

S4. Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 14 January 2016