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Asfotase Alfa: A Review in Paediatric-Onset Hypophosphatasia

Lesley J. Scott[1]

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Abstract Hypophosphatasia (HPP) is a rare inheritable disease that results from loss-of-function mutations in the *ALPL* gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). Therapeutic options for treating the underlying pathophysiology of the disease have been lacking, with the mainstay of treatment being management of symptoms and supportive care. HPP is associated with significant morbidity and mortality in paediatric patients, with mortality rates as high as 100 % in perinatal-onset HPP and 50 % in infantile-onset HPP. Subcutaneous asfotase alfa (Strensiq®), a first-in-class bone-targeted human recombinant TNSALP replacement therapy, is approved in the EU for long-term therapy in patients with paediatric-onset HPP to treat bone manifestations of the disease. In noncomparative clinical trials in infants and children with paediatric-onset HPP, asfotase alfa rapidly improved radiographically-assessed rickets severity scores at 24 weeks (primary timepoint) as reflected in improvements in bone mineralization, with these benefits sustained after more than 3 years of treatment. Furthermore, patients typically experienced improvements in respiratory function, gross motor function, fine motor function, cognitive development, muscle strength (normalization) and ability to perform activities of daily living, and catch-up height-gain. In life-threatening perinatal and infantile HPP, asfotase alfa also improved overall survival. Asfotase alfa was generally well tolerated in clinical trials, with relatively few patients discontinuing treatment and most treatment-related adverse events being of mild to moderate intensity. Thus, subcutaneous asfotase alfa is a valuable emerging therapy for the treatment of bone manifestations in patients with paediatric-onset HPP.

Asfotase alfa: clinical considerations in paediatric-onset hypophosphatasia
First-in-class enzyme replacement therapy
Provides sustained and rapid improvements in skeletal manifestations of HPP, based on Radiographic Global Impression of Change scores and Rickets Severity Scale scores
Improves pulmonary function, growth, physical function (normalizes skeletal muscle strength) and the ability to perform activities of daily living
The most common adverse reactions are injection-site reactions and injection-associated reactions, most of which are of mild to moderate intensity

1 Introduction

Hypophosphatasia (HPP) is a rare autosomal dominant or recessive disease and is currently classified into six different types: perinatal lethal HPP, prenatal benign HPP, infantile HPP (onset <6 months of age), childhood HPP

The manuscript was reviewed by: ***M. L. Bianchi***, Experimental Laboratory for Children's Bone Metabolism Research, Bone Metabolism Unit, Istituto Auxologico Italiano IRCCS, Milan, Italy ***C.R. Rockman-Greenberg***, Department of Paediatrics and Child Health, University of Manitoba, Winnipeg, Canada; ***C. Hofmann***, Children's Hospital University of Wurzburg, Wurzburg, Germany.

✉ Lesley J. Scott
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

(onset ≥6 months to 18 years of age), adult HPP (onset ≥18 years of age) and odonto-HPP (least severe form; is not associated with bone, articular or muscular problems) [1–3]. HPP is associated with significant morbidity and mortality in paediatric patients (onset <18 years of age), with mortality rates as high as 100 % in perinatal-onset HPP and 50 % in infantile-onset HPP [1, 2, 4–7]. The disease also imposes a high disease-burden in adult-onset HPP [6–8].

HPP results from loss-of-function mutations in the *ALPL* gene encoding tissue-nonspecific alkaline phosphatase (TNSALP), with at least 300 mutations identified to date (mostly missense mutations) [2, 7]. The more severe, life-threatening forms of HPP (severe perinatal and infantile forms) are generally associated with autosomal recessive inheritance (associated with mutations that suppress TNSALP activity almost completely), with milder forms inherited as autosomal recessive or dominant (associated with mutations that reduce TNSALP activity) [1, 2, 7]. The estimated prevalence of severe HPP in the general population is 1:100,000 [7, 9], but is much higher in some populations (e.g. Canadian Mennonites in whom the estimated prevalence is 1:2500 live births) [7, 10, 11]. The presentation and severity of the disease is highly variable; potential manifestations in paediatric-onset HPP include hypomineralization of bones and teeth, rickets, fractures, pulmonary insufficiency, failure to thrive, hypotonia, vitamin B6-responsive seizures, nephrocalcinosis, hypercalcaemia/hypercalciuria and craniosynostosis [7, 12]. Mutations in the *ALPL* gene result in a deficiency of TNSALP activity and consequently an increase in plasma levels of TNSALP substrates, including inorganic pyrophosphate (PPi; an excess of which retards hydroxyapatite crystal formation and thereby inhibits bone mineralization), pyridoxal 5′-phosphate (PLP; main circulating form of vitamin B6) and phosphoethanolamine [7, 12].

Currently, no curative options are available for the treatment of HPP, with management options for the most part involving symptomatic treatment, orthopaedic surgery and supportive care [1, 7, 12]. Symptomatic treatments for affected patients include lowering calcium intake to improve hypercalciuria, the use of nonsteroidal anti-inflammatory drugs for pain and the use of vitamin B6 in patients who experience seizures or are at risk of seizures (seizures are mainly present in severe perinatal HPP) [1, 7, 12]. However, worldwide there is a paucity/lack of treatments available for managing the underlying TNSALP defect, albeit various strategies have been investigated without success [7, 12]. Recently, the first pharmacological option aimed at treating the underlying pathophysiology of the disease, the bone-targeted enzyme-replacement therapy asfotase alfa (Strensiq®), was approved in the EU for long-term therapy in patients with paediatric-onset HPP to treat bone manifestations of the disease, including rickets/osteomalacia, altered calcium and phosphate metabolism, impaired growth and mobility and respiratory compromise that may require ventilation [13]. Asfotase alfa is approved in other countries for use in various forms of HPP, with this narrative review focusing on its clinical use in the EU.

2 Pharmacodynamic Properties of Asfotase Alfa

Asfotase alfa is a soluble 726 amino acid human recombinant TNSALP fusion protein (homodimer) consisting of the catalytic domain of human TNSALP, the human IgG Fc domain and a deca-aspartate bone-targeting peptide domain [14, 15]. In vitro studies showed that by adding an acidic oligopeptide of six or eight aspartate residues to a human recombinant C-terminal-anchorless TNSALP enzyme, the affinity of the human recombinant TNSALP enzyme for hydroxyapatite was enhanced 30-fold and retention of the tagged TNSALP enzyme in bone was fourfold greater than that of untagged TNSALP enzyme [16]. In cultured bone marrow from a patient with HPP, both tagged and untagged TNSALP enzymes were bioactive and initiated bone mineralization [16].

In vivo studies using a murine model of infantile HPP [TNSALP knockout mice ($Alpl^{-/-}$; also known as $Akp2^{-/-}$)] provide support for the use of asfotase alfa in the clinical setting [17–20]. In this model, daily subcutaneous asfotase alfa injections from birth prevented enamel defects and/or tooth loss, and improved mineralization in molar and incisor teeth in TNSALP knockout mice [17, 18, 20]. Treatment of TNSALP knockout mice from birth with asfotase alfa normalized growth and prevented the sequelae of HPP, such as skeletal and dental manifestations [19].

In patients with paediatric-onset HPP, asfotase alfa treatment is designed to promote bone mineralization and thereby improve skeletal structure [13]. The clinical efficacy of asfotase alfa in patients with paediatric-onset HPP is discussed in Sect. 4.

There is a potential for immunogenicity with asfotase alfa treatment [13]. Amongst 69 paediatric and adult patients with HPP enrolled in clinical trials who had post baseline data, 81.2 % had anti-drug antibodies at some point during asfotase alfa treatment. Of these 56 patients with anti-drug antibodies, 44.6 % (25 patients) also had neutralizing antibodies assessed in vitro. Regardless of whether neutralizing antibodies were present or not, the development of antibodies was time variant in nature. The development of anti-drug or neutralizing antibodies has not been shown to affect clinical efficacy or safety, with no patients with antibodies showing signs of hypersensitivity or tachyphylaxis following subcutaneous administration of asfotase alfa [13].

3 Pharmacokinetic Properties of Asfotase Alfa

Subcutaneous asfotase alfa exhibits linear pharmacokinetics up to dosages of 28 mg/kg/week, based on a population pharmacokinetic (PPK) analysis of data from all asfotase alfa clinical trials in patients with HPP ($n = 60$; age range 1 day to 66 years; 25 % of whom were >18 years of age) [13]. In this PPK analysis, bodyweight affected the volume of distribution and clearance of asfotase alfa, with exposure to asfotase alfa expected to increase with bodyweight, supporting a bodyweight-based dosage regimen (Sect. 6). Following subcutaneous administration, the absolute bioavailability of asfotase alfa was 60.2 %. The central and peripheral estimated clearance parameters in a 70 kg patient were 15.8 and 51.9 L/day, respectively. The average elimination half-life of subcutaneous asfotase alfa was 2.28 days [13].

4 Therapeutic Efficacy of Asfotase Alfa

The clinical development programme evaluating the use of subcutaneous asfotase alfa in paediatric-onset HPP included three ongoing, open-label, phase 2, multinational studies; namely the ENB-002-08 study and its ongoing extension (ENB-003-08), the ENB-006-09 study and its ongoing extension (ENB-008-10), and the ongoing ENB-010-10 trial [19]. Discussion focuses on these studies, which are supported by case studies [22, 23]. For selected endpoints, results from the ENB-006-09, ENB-002-08 and ENB-003-08 studies were compared with equivalently aged historical control cohorts. Some data are fully published [15, 24], with other data available as abstract, poster and/or oral presentations. These data are supplemented with information derived from the summary of product characteristics [13] and assessment report [21]. All participants in these trials had diagnosed documented HPP based on specified criteria and symptoms of the disease [21].

In the 6-month ENB-002-08 study ($n = 11$), infants aged ≤3 years (mean age 59 weeks [25]) with severe HPP (onset of symptoms occurred prior to 6 months of age) received an initial single intravenous infusion of asfotase alfa 2 mg/kg (one patient withdrew after this dose), followed by subcutaneous asfotase alfa three times a week at a dose of 1 mg/kg, with the dose adjusted up to 3 mg/kg based on efficacy [15]. At the end of this study, patients were eligible to enter the ongoing ENB-003-08 extension study ($n = 10$) [15]. In the ongoing ENB-010-10 study, children aged ≤5 years with HPP onset at less than 6 months of age received subcutaneous asfotase alfa 2 mg/kg three times a week or 1 mg/kg six times a week ($n = 60$ planned enrolments) [21, 26]. In the 6-month ENB-006-09 study, children aged 5–12 years of age with HPP onset at <6 ($n = 5$) or ≥6 ($n = 8$) months of age received subcutaneous asfotase alfa 2 mg/kg ($n = 6$) or 3 mg/kg ($n = 7$) three times a week [21]. At the end of the study, patients entered an ongoing extension study (ENB-008-10; $n = 12$) during which they initially received asfotase alfa 3 mg/kg/week; upon analysis of interim data, the dosage was increased to 6 mg/kg/week [21].

The primary endpoint in ENB-002-08, ENB-010-10 and ENB-006-09 was the change in skeletal manifestations of HPP at week 24 [15, 21, 26], assessed using the 7-point Radiographic Global Impression of Change (RGI-C) score [RGI-C scores range from −3 (i.e. severe worsening) to +3 (i.e. near-complete or complete healing)]. Rickets severity was also assessed using the 10-point Rickets Severity Scale (RSS), with higher scores indicating more severe disease [15, 21, 26]. In ENB-006-09, the comparison was with an age-matched historical control cohort [21]. Rickets severity was assessed by three independent radiologists, with a radiographic response defined as a minimum score of +2 (i.e. substantial healing) on the RGI-C scale [15, 21].

4.1 Effects on Skeletal Manifestations

4.1.1 Rickets Severity

After 24 weeks of asfotase alfa treatment, there were marked improvements from baseline in skeletal manifestations of HPP in the ENB-002-08, ENB-010-10 and ENB-006-09 trials, with these benefits maintained during long-term treatment in extension studies [15, 21].

In ENB-002-08/ENB-003-08, there were significant ($p = 0.004$) improvements in skeletal manifestations from baseline to week 24 and 48, based on RGI-C scores at week 24 (median score +2.0 points) and 48 (median score +2.3) [15]. These data were supported by improvements from baseline (median score 9.5) in RSS score at 24 (median reduction 3.5 points; $p = 0.004$; $n = 9$) and 48 weeks (median reduction 8.8; $p = 0.008$; $n = 9$). There was no deterioration in skeletal manifestations of HPP in patients treated with subcutaneous asfotase alfa for 6 months , whereas the patient who withdrew from treatment after a single intravenous dose showed a marked deterioration in skeletal manifestations of HPP at 14 months . At 6 months , skeletal improvements in asfotase alfa recipients included diffusely increased bone mineralization, corrected or improved endochondral and membranous bone formation, fracture healing, reduced deformity, resolution of redundancies and sclerosis, and extensive modelling and remodelling of bone [15].

Radiographically-assessed improvements from baseline in bone mineralization were sustained after 3 years of

asfotase alfa therapy in infants and children with severe HPP ($n = 9$ ongoing; ENB-003-08), with these improvements generally evident from 3 months (as assessed by RGI-C and RSS scores) [25]. Median RGI-C scores in evaluable patients ($n = 9$ and 8) at 2 and 3 years were +2 and +1.7 (both $p \leq 0.008$), with RGI-C responder rates at these respective timepoints of 100 and 75 %. Reductions in median RSS total scores over the 3-year period were consistent with RGI-C scores, with the median RSS total score reduced from 8.25 (severe rickets) at baseline to −6.50 at 2 years ($p = 0.008$) and −6.25 at 3 years ($p = 0.016$); scores at 2 and 3 years indicate a near absence of rickets [25].

Results from the ongoing ENB-010-10 study in infants and children ≤5 years of age (HPP onset at <6 months of age) support evidence from the ENB-002-08/ENB-003-08 study; one patient withdrew from treatment because of encephalopathy (considered unrelated to treatment) [27]. In an interim analysis, there were significant improvements in skeletal manifestations of HPP at 24 weeks (median RGI-C score +1.7; $p < 0.0001$; $n = 28$ evaluable), 48 weeks (median RGI-C score +2.0; $p < 0.0001$; $n = 19$) and 120 weeks (median RGI-C score +2.5; $p < 0.0001$; $n = 10$) [27].

In the ENB-006-09 study in older children with HPP, asfotase alfa significantly improved RGI-C and RSS scores at 6 months compared with age-matched historical controls who had undergone a similar protocol of clinical management, except with regard to asfotase alfa treatment [13, 28]. At 6 months RGI-C scores were +2 and +3 in asfotase alfa recipients, whereas these scores showed no significant change over time in the historical control group [13]. Improvements in skeletal manifestations of HPP were sustained in asfotase alfa recipients during ongoing treatment for up to 3 years (i.e. at last report; extension study ENB-008-10); at 2 years, the median improvement in RGI-C and RSS scores from baseline in asfotase alfa recipients was +2 ($p = 0.001$) and −2 ($p = 0.003$), with these improvements maintained at 3 years [28].

4.1.2 Bone Histology

After 24 weeks of asfotase alfa treatment, bone histology improved in ten per-protocol patients (excludes patients who received oral vitamin D between baseline and week 24) in the ENB-006-09 study in children aged 5–12 years [13]. After 24 weeks of asfotase alfa, the mean osteoid thickness was 9.5 μm (baseline 12.8 μm), the mean osteoid volume/bone volume was 8.6 % (baseline of 11.8 %) and the mean mineralization lag-time was 119 days (baseline 93 days) in biopsies of trans-iliac crest bone [13]. Bone mineral density Z-scores improved from baseline during 3 years of asfotase alfa treatment in the ongoing ENB-008-10 extension study in these children, albeit these improvements were not statistically significant ($n = 12$ evaluable) [29].

4.2 Survival Rate

The survival rate in 37 asfotase alfa-treated patients (≤5 years of age) enrolled in the ENB-002-08/ENB-003-08 and ENB-010-10 studies was compared with that of a historical cohort of patients with perinatal- or infantile-onset HPP ($n = 48$; ENB-011-10) [24]. Based on Kaplan-Meier estimates, asfotase alfa treatment significantly ($p < 0.001$) prolonged overall survival compared with the historical cohort, with the median survival time inestimable in the asfotase alfa group (as most patients were alive beyond the cutoff date) and 8.9 months (95 % CI 5.1–14.0) in the historical cohort. Survival rates at 1 and 5 years were 95 and 84 % in asfotase alfa recipients, with respective survival rates in the historical cohort of 42 and 27 % [24].

4.3 Effects on Respiratory Function

Respiratory function improved in all patients requiring respiratory assistance during 6 months of asfotase alfa treatment in the ENB-002-08 study, reflecting better mineralization of the rib cage during this period (Sect. 4.1) [15]. All patients had gracile or nonvisible ribs on baseline x-rays and, with the exception of one patient who could breathe ambient air, all patients exhibited some degree of respiratory compromise ranging from progressive insufficiency to requirement for full mechanical ventilation. At 48 weeks (ENB-003-08), the majority of patients (6 of 9) did not require ventilator support and were breathing ambient air; one patient required supplemental oxygen using a nasal cannula, one required mechanical ventilation at night and another patient was on full mechanical ventilation [15]. At 24 months, two of nine patients continuing asfotase alfa treatment required supplemental oxygen via a nasal cannula and one patient was receiving mechanical ventilation; the remaining patients did not require respiratory support [25]. By 30 months , one patient required supplemental oxygen and another mechanical ventilation, with no patients requiring mechanical ventilation at the last assessment timepoint of 42 months [25].

These data are supported by the ongoing ENB-010-10 study [27]. Most patients experienced improvements in pulmonary function after up to 120 weeks of asfotase alfa therapy in an interim analysis of 28 patients (15 of whom had received ≥12 months' treatment) [27]. During this period, 12 patients required no respiratory support at any time and 16 required respiratory support at some point (12 at baseline). At last assessment, eight patients had improved their respiratory status, of whom five patients no longer required respiratory support [27].

4.4 Effects on Growth, Physical Activity, Cognitive Function and Health-Related Quality of Life

In evaluable patients, seven of eight patients experienced improvements in age-equivalent scores for gross motor, fine motor and cognitive development in the ENB-002-08/ENB-003-08 study [assessed using the Bayley Scales of Infant Development (BSID)-III instrument] [15]. By 48 weeks, seven of nine patients were weight-bearing on their legs compared with no patients at baseline. Of these nine patients, four were walking/taking initial steps, one was standing, two were crawling and one was sitting up at 48 months [15]. In addition, approximately 50 % of patients (5 of 11) displayed apparent catch-up height-gain, albeit there were fluctuations in height-gain values, potentially reflecting the more severe disease and higher rate of morbidity in those younger patients [13]. At week 48, 96 and 144, the median Z-score for height had improved from baseline (-3.7; $n = 11$) by a median of $+1.2$ ($n = 9$), $+1.5$ ($n = 9$) and $+2.3$ ($n = 8$), respectively, in asfotase alfa recipients [30]. BSID-III gross motor scores also improved markedly from a score of 1 at baseline to 6 at 3 years [30].

In ENB-006-09/ENB-008-10 ($n = 13$), treatment with asfotase alfa was associated with persistent apparent catch-up height-gain in nine children and no apparent catch-up height-gain in three children, based on US Centers for Disease Control and Prevention growth charts for healthy age-matched children; one patient did not have enough data to permit judgement [13]. Progress through Tanner stages appeared appropriate. In the historical control cohort ($n = 16$), one patient displayed apparent catch-up height-gain, with no apparent catch-up height-gain observed in 12 patients and three patients having inconclusive data [13]. In asfotase alfa recipients, median height Z-scores progressively improved from a baseline of -1.3 to a score of -1.1, -0.8 and -0.8 at 6 months, 2 and 3 years, respectively [29].

In this ongoing extension study (ENB-008-10), children with HPP experienced rapid and sustained improvements in physical function, pain levels and the ability to participate in sports/recreation and activities of daily living during more than 3 years of asfotase alfa treatment [31, 32]. At baseline, enrolled children with HPP had poor strength and function compared with their healthy peers [31, 32]. During up to 3.5 years of asfotase alfa, right knee extensor and flexor strength (all $p \leq 0.002$ vs. baseline) and right hip extensor, flexor and abductor strength (all $p < 0.05$) improved in a clinically meaningful and statistically significant manner from baseline at all timepoints (at the last assessment point, seven and four patients had received 3 and 3.5 years' treatment); similar results were observed for muscle strength at the left knee and hip [32]. Values for knee and right hip abductors strength were within the normal range (80–100 %) at the last assessment timepoint. For example, median percent of predicted normal values for right knee extensor and flexor muscle strengths at baseline were 38 and 48 %, with these respective values increasing at 6 months (72 and 63 %), 12 months (74 and 77 %), 24 months (81 and 68 %) and the last assessment timepoint (98 and 93 %). At these timepoints, significant improvements in knee and hip strength were associated with continuous improvements in daily activities (such as running speed and agility), based on results of the Bruininks–Oseretsky Test of Motor Function Proficiency (BOT)-2 test. Normalization (i.e. within one standard deviation for BOT-2 scores) of muscle strength in asfotase alfa recipients started at month 6 and was sustained through to the last assessment, running speed and agility normalization occurred at 3 years, with normalization of the strength and agility composite score starting at 1 year [32]. These data for improvements in physical function and ability to undertake activities of daily living were supported by results from the parent-reported normative Pediatric Outcomes Data Collection Instrument (PODCI; at the last assessment point, eight and four patients had received 3 and 3.5 years' treatment) [31]. From 2 years onwards, most patients had no disability in terms of performing daily activities, with median Child Health Assessment Questionnaire (CHAQ) disability scores significantly ($p < 0.02$) decreased from 1.0 at baseline to 0.4, 0.3 and 0 at 0.25, 0.5 and 2 years, respectively [31]. Most patients were pain free from 3 months onwards; median CHAQ pain scores at baseline and 3 months were 20 and 0 ($p = 0.04$) [31].

4.5 Effects on Plasma Levels of TNSALP Substrates

Plasma PLP levels were significantly reduced from baseline (262 ng/mL; $n = 10$) at 24 (median change -244 ng/mL; $p = 0.004$; $n = 9$) and 48 (median change -182 ng/mL; $p = 0.016$; $n = 8$) weeks in infants in the ENB-002-08/ENB-003-08 study [15]. At baseline, plasma PLP levels were 2-fold to 18-fold higher than the upper limit of normal in ten of these patients and one patient was receiving pyridoxine treatment for vitamin B6-responsive seizures. There were also reductions from baseline in median plasma levels of PPi at 24 and 48 weeks (from 5.2 to 1.1 and 1.9 nmol/L, respectively; $n = 5$ evaluable), although these differences did not reach statistical significance [15].

5 Tolerability and Safety of Asfotase Alfa

Treatment-emergent adverse events observed in clinical trials of asfotase alfa were largely consistent with the manifestations and complications of underlying HPP or were injection-related reactions and most were of mild to moderate intensity, based on an integrated safety analysis of patients with perinatal/infantile-onset ($n = 48$),

juvenile-onset ($n = 20$), adult-onset ($n = 2$) or unknown age of onset ($n = 1$) HPP [21]. Very common (i.e. incidence ≥10 %) adverse reactions reported in clinical trials were headache, erythema, pain in extremity, injection site reactions, pyrexia, irritability and contusion [13]. Common (i.e. incidence ≥1 to <10 %) adverse reactions occurring in asfotase alfa recipients were injection site cellulitis, increased tendency to bruise, hot flush, hypoaesthesia oral, nausea, lipohypertrophy, cutis laxa, skin discolouration including hypopigmentation, skin disorder (stretched skin), myalgia, chills and scar [13].

The most common adverse reactions with asfotase alfa treatment were injection site reactions and injection-associated reactions, most of which were of mild to moderate intensity [13]. Approximately 73 % of patients in clinical studies experienced injection site reactions, most of which were of mild intensity and self-limiting. Injection site reactions resulted in a reduction in asfotase alfa dose in two patients and one patient discontinued treatment after a severe injection site reaction (injection site discolouration). Injection site reactions occurred more frequently in patients with juvenile-onset HPP and in patients receiving asfotase alfa injections six times a week (vs. 3 injections/week). Two patients experienced serious injection-associated reactions, with no discontinuation of asfotase alfa treatment; a patient with infantile-onset HPP experienced fever and chills, and a patient with juvenile-onset HPP experienced hypoaesthesia, pain in extremity, chills and headache [13].

Craniosynostosis, a clinical manifestation of HPP, occurred in 61.3 % of patients between birth and 5 years of age in a natural history study of untreated infantile-onset HPP [5]. In clinical trials of asfotase alfa treatment, adverse events of craniosynostosis (associated with intracranial pressure), including worsening of pre-existing craniosynostosis, have been reported in patients with HPP who are <5 years of age [13]. There are insufficient data to establish a link between asfotase alfa exposure and progression of craniosynostosis [13]. In the ENB-002-08/ENB-003-08 study, three patients had a history of craniosynostosis at baseline, with one of these patients having a further episode 128 days after starting asfotase alfa treatment [21]. In this study, four patients with no history of craniosynostosis at baseline experienced one or more episodes after ≥142 days of asfotase alfa treatment; all of these episodes were managed medically or surgically. Three patients at baseline in the ENB-006-09/ENB-008-10 study had a history of craniosynostosis treated surgically; none of these patients developed craniosynostosis during asfotase alfa therapy. In the ENB-010-10 study, there were five new cases of craniosynostosis after ≥8 weeks' exposure to asfotase alfa [21]. Periodic monitoring and prompt intervention for increased intracranial pressure is recommended in patients with HPP who are <5 years of age [13].

Ophthalmic (conjunctival and corneal) calcification and nephrocalcinosis, both of which are known manifestations of HPP, have been reported in clinical trials of asfotase alfa treatment [13]. There are insufficient data to establish a link between asfotase alfa exposure and ectopic calcification [13]. Nephrocalcinosis occurred in 51.6 % of patients between birth and 5 years of age in a natural history study of untreated infantile-onset HPP [5]. Periodic ophthalmology examination and renal ultrasounds are recommended in patients with HPP [13].

Serum parathyroid hormone levels may increase during asfotase alfa treatment in patients with HPP, especially during the first 12 weeks of treatment [13]. Monitoring of serum parathyroid hormone and calcium levels is recommended during asfotase alfa treatment and supplements of calcium and oral vitamin D may be required.

During asfotase alfa treatment, patients may experience disproportionate weight increase; dietary supervision is recommended [13].

6 Dosage and Administration of Asfotase Alfa

In the EU, subcutaneous asfotase alfa is indicated for long-term enzyme replacement therapy in patients with paediatric-onset HPP to treat bone manifestations of the disease, with approval granted under exceptional circumstances (Sect. 7) [13]. The recommended dosage of asfotase alfa is 2 mg/kg three times a week or 1 mg/kg six times a week. Asfotase alfa should only be administered subcutaneously and the maximum injection should not exceed 1 mL; if more than 1 mL is required, multiple injections may be administered at the same time. The safety and efficacy of asfotase alfa in patients with renal or hepatic impairment have not been studied and no specific dosage regimen can be recommended for these patients [13].

Local prescribing information should be consulted for detailed information, including drug interactions, precautions, warnings and use in specific patient populations.

7 Current Status of Asfotase Alfa in Paediatric-Onset Hypophosphatasia

HPP is a rare inheritable disease and, for those with paediatric-onset HPP, significantly impacts mortality and morbidity (Sect. 1). Therapeutic options for treating the underlying pathophysiology of the disease have been lacking, with the mainstay of treatment being management of symptoms and supportive care. Subcutaneous asfotase alfa, a bone-targeted human recombinant TNSALP replacement therapy, has had orphan drug status for the treatment of HPP in the EU since 2008 [33] and was recently approved in the EU for long-term

therapy in patients with paediatric-onset HPP to treat bone manifestations of the disease [13]. Under the exceptional circumstances for approval of asfotase alfa in the EU, the specific post-authorization measures required included: setting up a pharmacokinetic study in adults following administration of the dose advised in children; setting up a dose-response study to collect data on PPi and PLP; extending the ENB-008-10 and ENB-009-10 studies to provide efficacy data in patients aged 13–18 years; and setting up of an observational, longitudinal, prospective, long-term registry of patients with HPP to collect information on the epidemiology of the disease and to evaluate the safety and effectiveness data in patients treated with asfotase alfa [13]. The latter long-term registry of patients with HPP has recently been established to enable better characterization and understanding of the epidemiology and clinical course of HPP [34].

In noncomparative clinical trials in infants and children with paediatric-onset HPP, subcutaneous asfotase alfa rapidly improved radiographically-assessed RGI-C scores at 24 weeks (primary timepoint), as reflected in improvements in bone mineralization. These benefits were sustained after more than 3 years of treatment. Furthermore, patients typically experienced improvements in pulmonary function, gross motor function, fine motor function, cognitive development, catch-up height-gain (albeit with fluctuations), muscle strength (normalization) and the ability to perform activities of daily living. Asfotase alfa was generally well tolerated in clinical trials, with relatively few patients discontinuing treatment and most treatment-related adverse events being of mild to moderate intensity. Given the rarity of the disease, these trials involved a relatively limited number of patients and were of a noncomparative design. Based on these clinical trials, subcutaneous asfotase alfa is a valuable emerging therapy for the treatment of bone manifestations in patients with paediatric-onset HPP.

Data selection sources: Relevant medical literature (including published and unpublished data) on asfotase alfa was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 15 Dec 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Asfotase, ALXN-1215,ENB-040, Strensiq.
Study selection: Studies in patients with paediatric-onset hypophosphatasia who received asfotase alfa. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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