

**5.02 ASFOTASE ALFA RCH,
Injection, 18 mg in 0.45 mL, 28 mg in 0.7 mL, 40 mg in
1 mL and 80 mg in 0.8 mL, vial
Strensiq®, Alexion Pharmaceuticals Australasia Pty Ltd**

1 Purpose of Application

1.1 The submission requested a Section 100 (Highly Specialised Drugs Program), Authority Required PBS listing for asfotase alfa *rch* in the treatment of patients with paediatric-onset hypophosphatasia (HPP).

Table 1: Key components of the clinical issue addressed by the submission

Population	Patients with paediatric-onset HPP
Intervention	Asfotase alfa <i>rch</i> 6mg/kg/week via subcutaneous injection
Comparator	Best supportive care
Outcomes	6MWT and overall survival
Clinical claim	Asfotase alfa <i>rch</i> is superior in terms of comparative effectiveness and non-inferior in terms of comparative safety to best supportive care.

HPP = Hypophosphatasia; 6MWT = six-minute walk test
Source: Compiled during the evaluation

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (units)	№.of Rpts	Dispensed price per maximum quantity ^a		Proprietary Name and Manufacturer
			Public	Private	
ASFOTASE ALFA RCH					Strensiq® XI
Injection 18 mg in 0.45 mL, vial	12	0	\$ [REDACTED]	\$ [REDACTED]	
Injection 28 mg in 0.7 mL, vial	12	0	\$ [REDACTED]	\$ [REDACTED]	
Injection 40 mg in 1 mL, vial	12	0	\$ [REDACTED]	\$ [REDACTED]	
Injection 80 mg in 0.8 mL, vial	12	0	\$ [REDACTED]	\$ [REDACTED]	

^a Based on a requested ex-manufacturer price of \$ [REDACTED] per mg for public hospitals, with a \$40 mark-up and \$7.02 dispensing fee added for private hospitals.

Category / Program:	Section 100 – Highly Specialised Drugs Program
PBS Indication:	Paediatric-onset Hypophosphatasia (HPP)
Treatment phase:	Initial treatment
Restriction:	Authority required – in writing

Public Summary Document -July 2017 PBAC meeting

Clinical criteria:	<p>All infants 1 year old or younger with HPP, confirmed by age- and gender-adjusted alkaline phosphatase (ALP) activity below lower limit of normal and presence of HPP-related bone disease (by skeletal imaging), should be treated immediately.</p> <p>OR</p> <p>Patients with ALP activity below lower limit of age- and gender-adjusted normal range AND Patients with non-HPP-related causes of low ALP excluded AND Patients with available paediatric medical records documenting HPP-related symptoms AND Patients with a history of HPP-related bone disease, as assessed by skeletal imaging (radiography, dual energy x-ray absorptiometry [DXA] OR histomorphometry) PLUS ONE OR MORE of the following HPP-related morbidities:</p> <p>Respiratory compromise requiring mechanical ventilation or oxygen supplementation within the last 12 months OR</p> <p>Failure to thrive, within the last 12 months defined as a reduction in the z-score for weight of 1 SD or greater over the last 12 months OR</p> <p>Vitamin B₆-dependent seizures within the last 12 months OR</p> <p>Developmental delay; missed developmental milestones as defined by a validated scale within the last 12 months OR</p> <p>History of two or more non-traumatic, non-/poorly healing fractures requiring surgical fixation PLUS currently presenting with:</p> <p>Severely impaired mobility due to HPP-related skeletal deformities requiring assistance devices OR home modification AND</p> <p>Chronic muscular/joint and/or bone pain severe enough to limit the performance of activities of daily living/functional independence, requiring prescription pain medication.</p>
Prescriber Instructions	None proposed

Treatment phase:	Continuing treatment and grandfathered patients
Restriction:	Authority required in writing
Clinical criteria:	Evidence of clinical improvement or stabilisation of the patient's condition to support ongoing eligibility for asfotase alfa <i>rch</i> treatment*

* To satisfy these requirements, age-relevant clinical assessment scales utilised in the clinical development program for asfotase alfa *rch* should be administered, with evidence of clinical improvement/stabilisation based on changes in at least one of these scales (from pre-treatment/baseline, or from the last annual evaluation for those patients currently receiving subsidised asfotase alfa *rch*), utilising clinically relevant definitions of this improvement/stabilisation. Re-application by the treating physician to be submitted via a re-application by 1 May every year.

- 2.1 The restriction will require development in consultation with a rare diseases expert. The ESC questioned whether the restriction should include a requirement for genetic testing for the relevant mutations in the Alkaline Phosphatase, Liver/Bone/Kidney (ALPL) gene that can cause this condition.
- 2.2 The basis for the listing was a cost-utility analysis compared with best supportive care (BSC).
- 2.3 The recommended dosing regimen is either 1mg/kg six times a week, or 2mg/kg three times per week, via subcutaneous injection for the lifetime of the patient unless excluded from treatment by specified discontinuation criteria (e.g., failure to document treatment effectiveness, adverse events or non-compliance).
- 2.4 The submission proposed an annual expenditure cap through a risk sharing arrangement of \$ [REDACTED] per patient.

For more detail on PBAC's view, see section 7 "PBAC outcome."

3 Background

- 3.1 Asfotase alfa *rch* was TGA registered on 14 January 2016 as enzyme replacement therapy in patients with paediatric-onset HPP.
- 3.2 This is the first application to the PBAC for asfotase alfa *rch*.

4 Population and disease

- 4.1 Hypophosphatasia (HPP) is a rare disease. The disease presents as a continuum, with significant heterogeneity in morbidity and mortality. Signs and symptoms can appear at any time from before birth to adulthood, with several clinical forms currently recognised: (i) perinatal [onset before or at birth]; (ii) infantile [onset 0-6 months]; (iii) juvenile [onset 6 months - 17 years]; (iv) adult [onset 18+ years]; and (v) odonto-hypophosphatasia [only dental symptoms]. The submission appeared to define paediatric-onset HPP as disease with an onset of symptoms at less than 18 years of age, which would include perinatal-, infantile- and juvenile-onset HPP.
- 4.2 Generally, the earlier that symptoms are apparent, the more severe the form of the disorder. A patient's age at onset of symptoms is thought to reflect the level of enzymatic activity of tissue non-specific alkaline phosphatase (TNSALP) in an individual patient. In babies and infants, mortality is high, primarily due to respiratory failure as a result of defective bone mineralisation of the ribs. The disease can also result in rickets-like bone disease in infants and children and osteomalacia, kidney stones, raised intracranial pressure from premature craniosynostosis, nephrocalcinosis and pyridoxine-responsive seizures in patients of all ages.
- 4.3 Diagnosis is made based on medical history and clinical manifestations, confirmed following skeletal imaging consistent with HPP-related bone disease and a laboratory test showing low alkaline phosphatase (ALP) below the normal range for the patient's age and gender. Additionally, tests using commercially available assays for serum pyridoxal-5'-phosphate (PLP) or urine phosphoethanolamine (PEA), which are metabolic substrates of ALP, may be ordered and in patients with HPP these substrates would appear at levels above the upper limit of normal. Molecular genetic testing can also detect any of the 334 currently known different mutations in the ALPL gene that can cause this condition.
- 4.4 Asfotase alfa *rch* would be used in addition to best supportive care.

For more detail on PBAC's view, see section 7 "PBAC outcome."

5 Comparator

- 5.1 The submission nominated best supportive care (BSC) as the main comparator on the basis that there are no other therapeutic options that treat the underlying cause of HPP. The ESC considered this was the appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome."

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical cases and discussed the natural history of HPP and the use of asfotase alfa *rch* in patients noting the wide phenotypic variation in HPP. The presentation highlighted the benefits of asfotase alfa *rch* in assisting with mobility and improved quality of life, as well as mortality in infantile patients. The clinician and the Committee discussed prevalence rates (it was noted that the prevalence may be around 1:6000 (Mornet) if milder forms were included) and the applicability of genetic testing in Australia. The clinician briefly addressed concerns surrounding anaphylaxis and self-administration. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (6), health care professionals (6) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with asfotase alfa *rch* for HPP, including improved survival for infants, reduced pain, reduced disability, delayed disease progression and increased mobility.
- 6.3 The PBAC noted the advice received from Soft Bones Australia that outlined the likely use of asfotase alfa *rch* in clinical practice. The PBAC specifically noted the advice that the use of asfotase alfa *rch* may assist in preventing or improving the symptoms and complications associated with HPP. The comments noted symptoms can range from being very mild to life threatening and that diagnosing the condition can be difficult. While HPP is a genetic condition, the age at diagnosis can vary and many patients diagnosed as adults may have a history of symptoms throughout childhood. The comments indicated that subsidised access to asfotase alfa *rch* would be preferred for all forms of HPP, as opposed to just the requested population of paediatric-onset.
- 6.4 Representatives of the PBAC met with a representative of Soft Bones Australia prior to the PBAC meeting. The following is a summary of the perspectives presented to the PBAC representatives:
- HPP can be difficult to diagnose, particularly in patients with less severe symptoms, and can sometimes be mistaken for osteoarthritis or osteomalacia. Diagnosis is based on family background, symptoms and blood test results and can be confirmed with genetic testing (usually via the Unites States) which can take several months. Accordingly, the prevalence of HPP in Australia is uncertain.
 - The symptoms of HPP can affect quality of life for patients and their families/carers, impacting on their social, economic and psychological wellbeing. There is a spectrum of severity of symptoms, largely associated with limitations in physical growth, mobility, strength and stamina, both between patients and across a patient's lifetime.

- The most severely affected patients are a small group with perinatal/infantile-onset of symptoms who present with severe respiratory issues and may require mechanical ventilation or oxygen supplementation. As these patients age, their growth may be slower than expected and they may have significantly impaired movement. Consumers are of the view that treatment with asfotase alfa improves survival and may allow these patients to come off ventilation/oxygen earlier than otherwise expected. Life-long treatment with asfotase alfa is viewed as necessary to assist in building lung capacity, strength and mobility.
- Juvenile-onset patients may present with symptoms such as delayed growth, limitations in movement, fatigue, loss of teeth and rickets. Consumers are of the view that treatment with asfotase alfa can allow children to physically grow, improve independence in movement and build strength and stamina.
- Patients who either have adult-onset disease, or are diagnosed later in life with a history of less severe symptoms associated with HPP during childhood, may present with a range of symptoms such as arthritis, fractures, fatigue and neurological complications (described by the consumer representative as “brain fog”). Some of these older patients with symptoms during childhood may experience a “honeymoon period” in their 20s and 30s (which can further hamper diagnosis) but decline again in their 40s and 50s. Consumers are of the view that treatment with asfotase alfa can help to increase mobility and independence by increasing stamina, strengthening bones and healing fractures faster.

Clinical trials

- 6.5 The submission was based on:
- one head-to-head trial comparing asfotase alfa *rch* to best supportive care (n=19) ENB-009-10,
 - five supplementary non-randomised studies:
 - ENB-002-08 and extension study ENB-003-08;
 - ENB-10-10; and
 - ENB-006-09 and extension study ENB-008-10, and
 - a retrospective epidemiological review of patients receiving BSC (ENB-011-10).
- 6.6 The submission also presented data on a sponsored non-interventional natural history study (ALX-HPP-502 and a substudy of ALX-HPP-502) and a pooled analysis of studies ENB-002-08/ENB-003-08 with ENB-010-10 compared to ENB-011-10. Efficacy and safety results from ALX-HPP-502 were not used in the economic evaluation or used to support the clinical claim and therefore have not been presented here.
- 6.7 Details of the trials presented in the submission are provided in Table 2.

Public Summary Document -July 2017 PBAC meeting

Table 2: Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trials		
ENB-009-10	ENB-009-10: A randomized, open-label, multicenter, multinational, dose-ranging, concurrent control study of the safety, efficacy, and pharmacokinetics of asfotase alfa in adolescents and adults with Hypophosphatasia (HPP). Kishnani PS, Madson KL, Whyte MP, <i>et al.</i> Biochemical and physical function outcomes in adolescents and adults with hypophosphatasia treated with asfotase alfa for up to 4 years: Interim results from a Phase II study. Kishnani PS, Rockman-Greenberg C, Whyte M, <i>et al.</i> Enzyme replacement therapy (ENB-0040) decreases TNSALP accumulation and improves functional outcome in affected adolescents and adults. Whyte MP, Rockman-Greenberg C, Ozono K, <i>et al.</i> Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia.	2 April 2015 98 th Annual Meeting of the Endocrine Society (ENDO); April 1-4, 2016; Boston, MA. Abstract 25979. Presentation OR26-3 <i>Molecular Genetics and Metabolism</i> 2012;105(3):328-329 <i>J Clin Endocrinol Metab</i> 2016;101:334-42
Single arms of randomised trials with asfotase alfa <i>rch</i>		
ENB-006-09	ENB-006-09: A randomized, open-label, multicenter, multinational, dose-ranging, historical control study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of asfotase alfa in children with Hypophosphatasia (HPP). Whyte MP, Madson K, Phillips D, <i>et al.</i> Asfotase alfa therapy for children with hypophosphatasia.	3 April 2015 <i>JCI Insight</i> 2016;1(9):e85971
ENB-008-10	ENB-008-10: Extension study of protocol ENB-006-09 evaluating the long-term safety and efficacy of asfotase alfa in children with Hypophosphatasia (HPP). Whyte MP, Madson K, Phillips D, <i>et al.</i> Asfotase alfa therapy for children with hypophosphatasia.	3 April 2015 <i>JCI Insight</i> 2016;1(9):e85971
Nonrandomised single arm asfotase alfa <i>rch</i> studies		
ENB-002-08	ENB-002-08: A multicenter open-label study of the safety, tolerability, and pharmacology of ENB-0040 in up to 10 severely affected patients with infantile hypophosphatasia (HPP). Whyte MP, Greenberg CR, Salman NH, <i>et al.</i> Enzyme-replacement therapy in life-threatening hypophosphatasia.	6 April 2015 <i>N Engl J Med</i> 2012;366:904-13
ENB-003-08	ENB-003-08: Extension study of ENB-0040 in severely affected infants and young children with Hypophosphatasia (HPP). Simmons J, Bishop N, Fujita K, <i>et al.</i> Hypophosphatasia: Functional, skeletal and growth improvements in infants and young children treated with asfotase alfa for 5 years. Whyte, MP, Simmons JH, Lutz RE, <i>et al.</i> Enzyme-replacement therapy in life-threatening hypophosphatasia: The 3-year experience with asfotase alfa. Whyte MP, Greenberg CR, Salman NH, Bober MB, <i>et al.</i> Enzyme-replacement therapy in life-threatening hypophosphatasia. Bishop N, Simmons J, Lutz R, <i>et al.</i> Hypophosphatasia: Gross motor function and height improvement in infants and young children treated with asfotase alfa for up to 3 years. Whyte MP, Rockman-Greenberg C, Ozono K, <i>et al.</i> Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia.	6 April 2015 <i>ACMG Annual Clinical Genetics Meeting; March 8-12, 2016; Tampa, FL, USA. Abstract poster# 656</i> <i>Journal of Bone Mineral Research</i> 2014;29(Suppl 1). [Conference abstract] <i>N Engl J Med</i> 2012;366:904-13 <i>Horm Res Paediatr</i> 2014;82(suppl 1):29 <i>J Clin Endocrinol Metab</i> 2016;101:334-42
ENB-010-10	ENB-010-10: An open-label, multicenter, multinational study of the safety, efficacy, and pharmacokinetics of asfotase alfa in infants and children ≤ 5 years of age with Hypophosphatasia (HPP). Liese J, Hofmann C, Harmatz P, <i>et al.</i> Efficacy and Safety of Asfotase Alfa in	8 April 2015 Presented at: 98 th Annual Meeting

Public Summary Document -July 2017 PBAC meeting

	Patients with Infantile Hypophosphatasia Treated for up to 3.5 Years: Results from a Phase II, Open-Label, Uncontrolled Study. Whyte MP, Rockman-Greenberg C, Ozono K, <i>et al.</i> Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia.	of the Endocrine Society (ENDO); April 1-4, 2016; Boston, MA, USA. Abstract 25983. Presentation PP26-3J <i>Clin Endocrinol Metab</i> 2016;101:334-42
Best supportive care		
ENB-011-10	ENB-011-10: A retrospective non-interventional epidemiologic study of the natural history of patients with severe perinatal and infantile Hypophosphatasia (HPP). Whyte MP, Rockman-Greenberg C, Ozono K, <i>et al.</i> Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. Whyte MP, Leung E, Wilcox W, <i>et al.</i> Severe perinatal and infantile forms of hypophosphatasia: A retrospective natural history study. Whyte MP, Leung E, Wilcox W, <i>et al.</i> Hypophosphatasia: A Retrospective Natural History Study of the Severe Perinatal and Infantile Forms. Leung ECW, Mhanni AA, Reed M, <i>et al.</i> Outcome of perinatal hypophosphatasia in Manitoba Mennonites: A retrospective cohort analysis.	22 January 2014 <i>J Clin Endocrinol Metab</i> 2016;101:334-42 <i>J Inherit Metab Dis</i> 2014;37(Suppl 1):S175 [Conference abstract] Presented at the Pediatric Academic Societies Annual Meeting, May 3-5, 2014, Vancouver, Canada. <i>JIMD Reports</i> 2013;11:73-78

Source: Table B.2.3 and B.2.4, pp22-27 of Section B of the submission

As there were substantial differences in the characteristics of patients enrolled in the supportive studies, based on differing inclusion and exclusion criteria, results between studies were not comparable. However, the submission indicated that an overall survival analysis was undertaken for patients from ENB-002-08/ENB-003-08 and ENB-010-10 who were 5 years or less at enrolment, who had documented diagnosis of HPP, onset of signs before 6 months of age, and documentation of characteristics of perinatal/infantile onset HPP used to define 'high-risk of premature death'. *While results may be comparable across these patient groups, it was not clear how or why these particular patients were selected for inclusion in an overall survival analysis while others were not.*

6.8 The key features of the included trials and studies are summarised in Table 3.

Public Summary Document -July 2017 PBAC meeting

Table 3: Key features of the included evidence, asfotase alfa rch vs. best supportive care

Trial	N	Treatment arms	Trial design	Risk of bias	Primary outcome	Use in the economic evaluation
ENB-009-10	13 6	Asfotase alfa <i>rch</i> , Concurrent control group*	OL, R*	Low	<ul style="list-style-type: none"> Effect of AA on reduction in plasma PPI and PLP levels Tolerability of daily SC injections of AA 	Primary outcome: Not used Other outcome of change in 6MWT used
ENB-002-08	11	Asfotase alfa <i>rch</i>	OL	High	<ul style="list-style-type: none"> Efficacy of AA in treating skeletal manifestations of infantile HPP Safety and tolerability of AA given IV in a single dose and by SC in repeat doses 	Primary outcome: Not used Other outcome of overall survival and invasive ventilator-free survival used in pooled comparative analysis
ENB-003-08					<ul style="list-style-type: none"> Long-term efficacy of AA in treating rickets in infants and young children with HPP Long-term tolerability of SC AA 	
ENB-010-10	59	Asfotase alfa <i>rch</i>	OL	High	<ul style="list-style-type: none"> Effect of AA on skeletal manifestations of HPP Safety and tolerability of repeated SC injections of AA 	Primary outcome: Not used Other outcome of overall survival and invasive ventilator-free survival used in pooled comparative analysis
ENB-006-09	13 16	Asfotase alfa <i>rch</i> Historical control group	OL	High	<ul style="list-style-type: none"> Effect of AA in treating HPP-related rickets as compared to historical controls Safety and tolerability of AA 	Primary outcome: Not used Other outcome of change in 6MWT used for AA patients
ENB-008-10					<ul style="list-style-type: none"> Long-term tolerability of SC AA Proportion of AA-treated patients showing radiographic change in rickets severity from the Baseline of ENB-006-09 relative to the end of study visit 	
ENB-011-10	48	Best supportive care	RR	High	<ul style="list-style-type: none"> Overall survival 	Used in comparative analysis of overall survival and invasive ventilator-free survival
ALX-HPP-502	32	Best supportive care	RR	High	<ul style="list-style-type: none"> Skeletal manifestations of HPP measured by using the RGI-C score Growth measured by change in height Z scores 	Not used
ALX-HPP-502 substudy	6	Best supportive care	RR	High	<ul style="list-style-type: none"> Gait performance evaluated from recorded video measured by the MPOMA-G 	Not used

* Concurrent control group for the first 24 weeks of the trial

OL=open-label; R=randomised; RR=retrospective review; RGI-C = radiographic global impression of change; MPOMA-G = modified performance-oriented mobility assessment; 6MWT = six-minute walk test; PLP = pyridoxal 5'-phosphate; PPI = inorganic pyrophosphate; AA = asfotase alfa *rch*; HPP = hypophosphatasia; SC =subcutaneous; IV = intravenous

Source: compiled during the evaluation

6.9 While the pivotal trial, ENB-009-10, was open-label, the objective outcomes of reduction in plasma pyridoxal 5'-phosphate (PLP) and inorganic pyrophosphate (PPI) levels were not likely to have been influenced by any bias associated with knowledge of treatment allocation.

6.10 The economic model was based on the outcome of changes in the six-minute walk test (6MWT), overall survival and invasive ventilator-free survival, as detailed in

Table 3. The ESC noted that none of the clinical trials presented used the 6MWT as a primary outcome, therefore, the economic model was reliant on secondary outcomes or post-hoc analyses.

- 6.11 The direct randomised trial ENB-009-10 did not include overall survival or invasive ventilator-free survival as an outcome, and the primary outcome from this trial of the effect of asfotase alfa *rch* on reducing plasma pyridoxal 5'-phosphate (PLP) and inorganic pyrophosphate (PPi) levels was not used in the economic model. Results of change in 6MWT distance from Trial ENB-009-10 were used in the economic model in conjunction with results for this outcome from Trial ENB-006-09/ENB-008-10 (after transformation by the submission), however it was not clear in the submission where the results for change in 6MWT distance for the BSC treatment group were derived. The submission's use of change in 6MWT distance as a proxy for disease state severity for patients with HPP may not capture other important aspects of HPP such as skeleton and joint deformity and renal and neurological complications. The PSCR (p2) argued that the 6MWT is a clinical measure of disease severity and treatment response in HPP. The PSCR also cites the 6MWT has been used to support regulatory approval and reimbursement of enzyme replacement therapies such as laronidse and idursulfase in MPS I and MPS II. The ESC considered that the use of the 6MWT as a surrogate outcome was inadequately supported for this condition.
- 6.12 Given the small patient numbers available in the direct randomised trial and the short 24 week time frame for the randomised component of the trial, it was appropriate for the submission to also present data on non-randomised studies of asfotase alfa *rch* and BSC. However, differences in the eligibility criteria and baseline characteristics in these studies (including age, age of onset of symptoms, disease severity and clinical manifestations) meant that the results from the studies were not comparable.
- 6.13 The ESC considered the data supporting clinical benefit was deficient and little justification was provided to correlate biochemical measurement improvements with clinically relevant outcomes or clinically meaningful improvement.

Comparative effectiveness

- 6.14 The primary outcome of trial ENB-009-10 was change from baseline to 24 weeks in PLP and PPi. At Week 24, there was a statistically significant difference between asfotase alfa *rch* and BSC in the primary outcome of reducing PLP ($p=0.0285$). Excluding a control patient who received a high dose of vitamin D and who had a high baseline PPi level, there was also a statistically significantly greater reduction in PPi levels for patients treated with asfotase alfa *rch* compared to BSC at Week 24 ($p=0.0044$). The decreases in PLP and PPi were maintained in asfotase alfa *rch* treated patients after Week 48 and 96 of exposure.
- 6.15 The results of the 6MWT from the direct randomised trial and supportive studies are summarised in Table 4.

Table 4: Change in 6MWT results from the direct randomised trial and supportive studies

		ENB-009-10		ENB-006-09/ ENB-008-10	
		Asfotase alfa <i>rch</i>	BSC ^a	Asfotase alfa <i>rch</i>	Historical control
N		13/19 ^b	6	13	16
Change from baseline in 6MWT distance, mean metres (SD)	Baseline	409.9 (139.5)	217.8 (218.9)	345 (90.5)	
	Week 24	54.9 (59.7)	13.5 (70.0)	██████████	
	p=0.1303				
	Week 48	██████████	██████████	██████████	
	Week 96	██████████	██████████	██████████	
	Week 144	██████████	██████████	██████████	
	Week 192	██████████	██████████	██████████	
Change from baseline in 6MWT distance, per cent of predicted, mean metres (SD)	Baseline	73.33 (19.86)	76.93 (16.66)	59.06 (14.96)	
	Week 24	██████████	██████████	19.38 (10.5)	
	Week 48	██████████	██████████	22.20 (9.1)	
	Week 96	██████████	██████████	20.80 (10.5)	
	Week 144	██████████	██████████	30.60 (10.8)	
	Week 192	██████████	██████████	25.28 (15.1)	
	Week 240	██████████	██████████	23.24 (13.7)	

^a Placebo group crossed-over to AA at week 24

^b 13/19: Results at week 192 are for 13 patients, results reported for 19 patients at all other time points (due to BSC patients crossing-over to asfotase alfa *rch* at Week 24)

BSC = best supportive care; SD = standard deviation; nr = not reported

Source: compiled during the evaluation from Tables B.6.2-B.6.17, pp102-207 of Section B of the submission

6.16 The submission estimated the minimal clinically important difference (MCID) for the change in 6MWT in children with HPP aged 5-12 years to be 30.2 metres (based on using the one-third standard deviation (SD) distribution-based approach, which was said to represent 8.8% of the mean baseline distance walked). The same methodology was previously reported in the literature for estimating a MCID for the 6MWT in boys with Duchenne muscular dystrophy (28.5 to 31.7 metres, or 8.9%).

6.17 The difference in mean 6MWT distance as per cent predicted from Baseline to Week 24 for patients treated with asfotase alfa *rch* treated compared with BSC was not statistically significant (p=██████████). In terms of the overall mean change in 6MWT distance from Baseline to Week 24 (without conversion to per cent predicted), there was a difference of ██████ metres. While Trial ENB-009-10 showed that asfotase alfa *rch* improved mean 6MWT distance by more than the proposed MCID of 30.2 metres compared with BSC, this difference was also not statistically significant (p=0.1303). In Trial ENB-009-10, the difference in 6MWT at Week 144 (the last reported 6MWT in the BSC arm) was ██████ metres, which was also not statistically significant. The submission attributed the lack of statistical significance to significant heterogeneity in baseline values and treatment responses, as well as the small sample sizes, with the submission stating that the trial wasn't powered to detect specific changes in the 6MWT. Overall, there was insufficient evidence to demonstrate that asfotase alfa *rch* improved 6MWT distance, compared with patients treated with BSC, from this trial.

6.18 The submission presented a pre-specified analysis of overall survival from trials ENB-002-08/ENB-003-08 and ENB-010-10 in patients with perinatal-/infantile-onset HPP (defined as onset of symptoms prior to 6 months) who were at high risk of premature death (as defined by the presence of respiratory compromise, vitamin B6

responsive seizures and/or rachitic chest deformity). This was compared with overall survival among a matched, non-concurrent untreated historical control group from Trial ENB-011-10. Results for overall survival are detailed in Table 5 for the full survival analysis (which enrolled 68 asfotase alfa *rch* patients). Figure 1 presents the Kaplan-Meier survival curve for this analysis.

6.19 The submission also presented two sensitivity analyses for the death rate (summarised in Table 5) given that the analysis was subject to the following two sources of bias (i) differences in the dates of the studies and year of diagnosis; and (ii) the historical control patients in the analysis included all patients from the time of their diagnosis, whereas the asfotase alfa *rch* treated patients only included patients who survived to enrolment in the trial.

Table 5: Overall survival

	Asfotase alfa <i>rch</i> pooled result ^a (n=68)	Historical controls ENB-011-10 (n=48)	p-value
OS: Median survival time from birth (days); 95% CI	7211; (N/A)	270.5; (155, 428)	≤0.0001
OS: proportion of patients dying ^b	████████	35 (72.9%)	≤0.0001
Sensitivity analyses			
OS: proportion of patients dying, BSC patients diagnosed after 2000	████████	████████	████████
OS: proportion of patients dying, BSC patients surviving to week █████	████████	████████ (████%)	████████

^a Combined results of ENB-002-08/ENB-003-08 and ENB-010-10

^b Patients with perinatal/-infantile-onset HPP only

BSC = best supportive care; N/A = not applicable; OS = overall survival

Source: compiled during the evaluation from Tables B.6.2-B.6.17, pp102-207 of Section B of the submission

Figure 1: Kaplan-Meier plot of overall survival in asfotase alfa *rch* treated patients from ENB-002-08/ENB-003-08 and ENB-010-10) versus untreated historical control patients from ENB-011-10 at high risk of mortality from perinatal-/infantile-onset HPP



6.20 All survival analyses presented by the submission indicated that treatment with asfotase alfa *rch* resulted in improved survival. Overall, while it appeared that

Public Summary Document -July 2017 PBAC meeting

treatment with asfotase alfa *rch* may have improved overall survival in patients with perinatal/infantile-onset HPP at high risk of death compared with matched historical control patients, the analysis was considered to be subject to considerable bias. Of further consequence to the reliability of the estimates was that as it was not clear what the data sources were, as the submission cited Whyte et al 2015 and Leung et al 2013, and neither of these sources reported these results. Therefore, it was not possible to have confidence in the extent of the overall survival benefit as calculated by the submission.

6.21 No overall survival data was reported for juvenile-onset HPP. The pre-PBAC response clarified that the sponsor did not evaluate a survival benefit for asfotase alfa *rch* in patients with juvenile-onset HPP as the clinical manifestations in this cohort do not cause short-term mortality.

6.22 Quality of life was measured in some of the trials and studies, using different questionnaires, as summarised in Table 6.

Table 6: Quality of life results from the direct randomised trial and supportive studies

		ENB-009-10		ENB-006-09/ENB-008-10	
		Asfotase alfa <i>rch</i>	BSC ^a	Asfotase alfa <i>rch</i>	Historical control
N		13	6	13	16
Quality of life; change from baseline to Week 24; mean (SD)	LEFS	██████████	██████████	Nr	
		██████████	██████████	Nr	
	BPI-SF	██████████	██████████	Nr	
		██████████	██████████	Nr	
	CHAQ; mean disability score	nr	Nr	-0.6364 (0.62); p=0.0068	
PODCI; parent assessed	nr	Nr	██████████		

^a Placebo group crossed-over to AA at week 24

BSC = best supportive care; SD = standard deviation; PODCI = paediatric outcomes data collection instrument; CHAQ = childhood health assessment questionnaire; nr = not reported; LEFS = lower extremity functional scale; BPI-SF = brief pain inventory – short form; Source: compiled during the evaluation from Tables B.6.2-B.6.17, pp102-207 of Section B of the submission

6.23 There was no statistically significant difference in mean change in quality of life from Baseline to Week 24, as measured by the Lower Extremity Functional Scale (LEFS) or the Brief Pain Inventory-Short Form, for patients treated with asfotase alfa *rch* compared with BSC in Trial ENB-009-10.

6.24 Quality of life was also assessed using the Paediatric Outcomes Data Collection Instrument (PODCI) and the Childhood Health Assessment Questionnaire (CHAQ) in Trial ENB-006-09/ENB-008-10. Based on an in-group comparison of the change from Baseline for asfotase alfa *rch* treated patients at Week 24, there was an improvement in the mean CHAQ disability score of -0.6364, and an improvement in the PODCI, as assessed by parents, of ██████████. The difference from Baseline to Week 24 was statistically significant. The results suggested that asfotase alfa *rch* may improve quality of life. However, the results were insufficient to support a claim that treatment with asfotase alfa *rch* improves quality of life compared with BSC.

Comparative harms

6.25 The submission did not provide statistical analyses for the adverse events reported in Trial ENB-009-10. From the statistical analysis undertaken during the evaluation, there was a statistically significant difference between patients treated with asfotase alfa *rch* compared with BSC in relation to “General disorders & administration site conditions” (with preferred terms inclusive of injection site reactions, including injection site erythema, injection site haematoma, injection site pain, injection site pruritus, injection site discolouration, and injection site swelling) with the majority [REDACTED] % of patients treated with asfotase alfa *rch* reporting this ([REDACTED]) compared with [REDACTED] % of patients treated with BSC ([REDACTED] (risk difference 60.3% [95%CI: 11%, 85%]). There were no statistically significant differences observed between the treatment groups for any other reported adverse events.

Benefits and harms

6.26 A summary of the comparative benefits and harms for asfotase alfa *rch* versus BSC from Trial ENB-009-10 is presented in Table 7.

Table 7: Summary of comparative benefits and harms for asfotase alfa *rch* and best supportive care

Benefits							
Change from baseline in PPI							
Trial	Asfotase alfa <i>rch</i>			Best supportive care			Mean difference: Asfotase alfa <i>rch</i> vs. best supportive care
	N	Mean Δ baseline PPI at Week 24 (μ M)	SD	n	Mean Δ baseline PPI at Week 24 (μ M)	SD	
ENB-009-10	13	-2.10	1.33	6	-1.05	2.92	-1.05 (p=0.0715 ^a)
Change from baseline in PLP							
Trial	Asfotase alfa <i>rch</i>			Best supportive care			Mean difference: Asfotase alfa <i>rch</i> vs. best supportive care (ng/mL)
	N	Mean Δ baseline PLP at Week 24 (ng/mL)	SD	n	Mean Δ baseline PLP at Week 24 (ng/mL)	SD	
ENB-009-10	13	-397.72	455	6	26.80	264	-370.92 (p=0.0285)
Harms							
	Asfotase alfa <i>rch</i>	Best supportive care	RR (95% CI)	Events/100 patients over 24 weeks		RD (95% CI)	
				Asfotase alfa <i>rch</i>	Best supportive care		
General disorders and administration reactions							
ENB-009-10	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	0.60 (0.11, 0.85)

^a Excluded patient who ingested a high dose of Vitamin D (25,000 IU) 23 days prior to sampling; p= 0.0044

SD = standard deviation; RR = relative risk; RD = risk difference; PLP = pyridoxal 5'-phosphate; PPI = inorganic pyrophosphate; nr = not reported

Source: compiled during the evaluation

6.27 On the basis of direct evidence presented by the submission, the comparison of asfotase alfa *rch* and best supportive care resulted in approximately a 1.05 μ m reduction in PPI and a 371 ng/mL reduction in PLP over a mean duration of exposure of 24 weeks. However, the submission did not indicate what change in PPI and PLP would be clinically meaningful to the patient (although the submission stated that the results implied that asfotase alfa *rch* has a direct effect on the underlying disease

pathophysiology of HPP, and that it should be expected to have a positive effect on bone mineralisation and skeletal structure).

- 6.28 On the basis of direct evidence presented by the submission, for every 100 patients treated with asfotase alfa *rch* in comparison to best supportive care, approximately 60 additional patients would experience “General disorder & administration site conditions” over a mean duration of exposure of 24 weeks.
- 6.29 No statistically significant differences in the 6MWT were observed in Trial ENB-009-10 between asfotase alfa *rch* and BSC over a mean duration of exposure of 24 weeks.

Clinical claim

- 6.30 The submission described asfotase alfa *rch* in paediatric-onset HPP as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over best supportive care.
- 6.31 The submission demonstrated a significant difference in relation to the primary outcome of reduction in PPI and PLP levels in the randomised comparative trial ENB-009-10 at the pre-specified endpoint of Week 24. The submission stated that these results implied that asfotase alfa *rch* has a direct effect on the underlying disease pathophysiology of HPP and that it should be expected to have a positive effect on bone mineralisation and skeletal structure. However, the submission did not indicate what difference in PPI and PLP would be clinically meaningful for patients.
- 6.32 In considering overall survival and improvement in the 6MWT distance per cent predicted, the ESC considered that the submission’s claim of superiority in comparative effectiveness was not adequately supported for the entire population of patients with paediatric-onset HPP for the following reasons:
- In the absence of concurrent control groups in all but one of the prospective trials, a comparison to historical controls was subject to potential bias and considerable uncertainty;
 - Baseline characteristics were not available for some of the historical control patients, making a meaningful comparison difficult;
 - The submission did not demonstrate statistically significant differences in terms of observed/predicted 6MWT distance for patients treated with asfotase alfa *rch* compared with BSC;
 - Overall survival data was only reported for perinatal- and infantile-onset HPP (onset before or at birth, to 6 months of age). No overall survival data was reported for juvenile-onset HPP (6 months - 17 years);
 - The submission did not address the validity of using a surrogate (6MWT) to final, patient relevant, outcomes in line with the PBAC Guidelines V5.0; and
 - Overall, the clinical evidence presented did not provide a strong estimate of the size of the benefit or a good indication of the likely variation in the effect of treatment.

- 6.33 The submission did not show non-inferiority in terms of comparative safety as there was a greater number of “General disorders & administration site conditions” for patients treated with asfotase alfa *rch* compared to best supportive care in Trial ENB-009-10. Additionally, there are limited long-term efficacy or safety data for asfotase alfa *rch*.
- 6.34 The PBAC considered that the claim of superior comparative effectiveness, in terms of improved overall survival for patients with perinatal- and infantile-onset who were at high risk of premature death (as defined by the presence of respiratory compromise, vitamin B6 responsive seizures and/or rachitic chest deformity) was reasonable. However, the magnitude of the survival benefit was unclear given the study design was associated with a high risk of bias.
- 6.35 The PBAC acknowledged that asfotase alfa appears to reduce PPI and PLP levels; however, it was unclear what magnitude of changes would be clinically meaningful for patients. In addition, the submission did not demonstrate statistically significant differences in terms of observed/predicted 6MWT distance for patients treated with asfotase alfa *rch* compared with BSC. Accordingly, the PBAC considered that the claim of superior comparative effectiveness, in terms of an improvement in morbidity for juvenile-onset HPP, was not adequately supported by the submission.
- 6.36 The PBAC noted that there was a significant increase in “general disorder and administration site conditions” for patients treated with asfotase alfa *rch*, compared with BSC, and therefore considered that the claim of non-inferior comparative safety was not supported by the data.

Economic analysis

- 6.37 The submission presented a stepped economic evaluation that included a cost-effectiveness analysis (incremental cost per additional metre walked in the 6MWT in the ENB-009-10 trial from Baseline to 24 weeks), and modelled cost-utility analysis. A summary of the structure and rationale for the modelled cost-utility analysis is presented in Table 8.

Table 8: Summary of model structure and rationale

Component	Summary								
Time horizon	101 years in the model base case versus up to 54 months for asfotase alfa <i>rch</i> in the trials, and up to 15 years for best supportive care in the natural history studies								
Outcomes	Mean change in 6MWT distance from Baseline, as per cent of predicted distance at 240 weeks and QALYs								
Methods used to generate results	Markov transition model								
Health states	The model included four alive health states (Severity levels I, II, III and IV) and two dead states (HPP death, which was only relevant in the analyses including those aged ≤4 years, and overall death). The alive health states for severity levels I-IV were defined based on two times the estimated MCID calculated for the per cent predicted distance on the 6MWT derived for Duchenne muscular dystrophy (DMD) of 8.9% (see below).								
	<table border="1"> <thead> <tr> <th>Alive health states</th> <th>Definition</th> </tr> </thead> <tbody> <tr> <td>Severity level I</td> <td>6MWT score >82.2% of predicted value</td> </tr> <tr> <td>Severity level II</td> <td>82.2%≥ 6MWT score >64.4% of predicted value</td> </tr> <tr> <td>Severity level III</td> <td>64.4%≥ 6MWT score >46.6% of predicted value</td> </tr> </tbody> </table>	Alive health states	Definition	Severity level I	6MWT score >82.2% of predicted value	Severity level II	82.2%≥ 6MWT score >64.4% of predicted value	Severity level III	64.4%≥ 6MWT score >46.6% of predicted value
Alive health states	Definition								
Severity level I	6MWT score >82.2% of predicted value								
Severity level II	82.2%≥ 6MWT score >64.4% of predicted value								
Severity level III	64.4%≥ 6MWT score >46.6% of predicted value								

Public Summary Document -July 2017 PBAC meeting

	<p>Severity level IV 6MWT score \leq46.6% of predicted value</p> <p>6MWT = six-minute walk test Source: Table C.4.1, p16 of Sections C to F of the submission</p> <p>It was not apparent that the submission's use of the 6MWT was reliable for defining the severity health states as the 6MWT would not capture additional clinical features of HPP such as skeleton and joint deformity and renal and neurological complications.</p> <p>Further, the reliability of the use of an MCID that was based on patients with DMD rather than for patients with paediatric-onset HPP was uncertain, given that DMD is a progressive disease with a short life-expectancy and HPP survival beyond childhood appears to be normal. There was little reason to assume that the MCID thresholds would be the same for both conditions, however it is noted that the MCID estimated for HPP was only slightly different, at 8.8%.</p>										
Utilities	<p>The utilities applied to the alive health states are summarised below.</p> <table border="1"> <thead> <tr> <th>Alive health states</th> <th>Utility</th> </tr> </thead> <tbody> <tr> <td>Severity level I</td> <td>0.86</td> </tr> <tr> <td>Severity level II</td> <td>0.67</td> </tr> <tr> <td>Severity level III</td> <td>0.54</td> </tr> <tr> <td>Severity level IV</td> <td>0.23</td> </tr> </tbody> </table> <p>Source: Table C.5.1, pp30-31 and Table C.5.5, p32 of Sections C to F of the submission</p> <p>Utilities were elicited from nine clinicians in the UK/Canada/Germany based on a description of the various health states. In contrast to the submission's approach of building the economic model on alive health states based on changes in 6MWT distance, the submission indicated that for the derivation of utility values that utility scores based on the 6MWT would not adequately capture all the HPP symptoms/complications impacting on quality of life. While this was considered to be true, the submission's approach lacked consistency and coherence: on the one hand the submission argued that it was acceptable to build an economic model with transitions between alive health states based on changes in 6MWT distance, and then on the other hand the submission argued that utility values for those health states should not be based on changes in 6MWT distance but on a broader description of the health state.</p> <p>The case descriptions presented to clinicians did not correlate well with the characteristics of patients assigned to each alive health state. For example, while case description 3 indicated that a patient in Severity level III would have 'occasional respiratory problems' and case description 4 indicated that a patient in Severity level IV would have 'prolonged respiratory infections', the prevalence of these conditions was 59% for respiratory compromise versus 50% for patients in Severity level III versus IV, respectively.</p>	Alive health states	Utility	Severity level I	0.86	Severity level II	0.67	Severity level III	0.54	Severity level IV	0.23
Alive health states	Utility										
Severity level I	0.86										
Severity level II	0.67										
Severity level III	0.54										
Severity level IV	0.23										
Cycle length	12 weeks; a half-cycle correction was applied for the first and last cycle										
Transition probabilities	Derived from the regression function in the multivariate ordered probit model including covariates for patient age (years) at the time of the current visit, and the interactions of age and prior severity level. The transition probabilities were derived from very few observed 6MWT transitions in the studies (i.e., n=34 for BSC and n=250 for asfotase alfa <i>rch</i>) and were applied consistently in the model over a time horizon of 101 years.										

6MWT = six-minute walk test; QALYs = quality adjusted life years saved
Source: constructed during the evaluation

Public Summary Document -July 2017 PBAC meeting

6.38 Key drivers of the economic evaluation are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Changes in 6MWT distance assumed from trial data and extrapolated out to a lifetime model with treatment effect (not shown to be significant in Trial ENB-009-10) assumed to continue out beyond the 54 month duration of the trial to 101 years.	High, favours asfotase alfa <i>rch</i>
	A Weibull curve was fitted to the overall survival data for patients with perinatal/infantile-onset HPP from trials ENB-002-08/ENB-003-08 and ENB-010-10, while the submission stated that overall survival wasn't extrapolated. The submission assumed that the increased overall survival seen in patients with symptoms prior to 6 months of age compared with historical controls from Trial ENB-011-10 would continue, with no increased risk of mortality compared with BSC as a patient ages.	Moderate, favours asfotase alfa <i>rch</i>
	Progression in disease severity , as observed by changes in 6MWT for patients aged ≥5 years, could be extrapolated to characterise the severity of the disease for patients aged <5 years. Changes in 6MWT distance may not reflect changes in disease state severity, especially for patients aged less than 5 years.	Moderate, favours asfotase alfa <i>rch</i>
Alive health states	It was not apparent that health states defined by per cent predicted 6MWT adequately represented all alive patients with paediatric-onset HPP given other symptoms associated with the condition may not be captured by this measure.	Moderate, favours asfotase alfa <i>rch</i>
Utility gained from the change in 6MWT from baseline	The utility values applied to Severity levels I-IV and their method of derivation are presented in Table 8, respectively. While a disutility for invasive ventilation of -0.33 was also applied, the submission did not use the derived values of 0.24 for all children aged 5 years or less not on invasive ventilation or -0.09 for children aged 5 years or less on invasive ventilation (choosing to test a value of 0.24 in a sensitivity analysis for this age group). It was not apparent that there would be an improvement in utility values for patients treated with asfotase alfa <i>rch</i> , as there wasn't a significant difference in quality of life compared to BSC shown in the direct randomised trial ENB-009-10. It was also not apparent that utility values for newborns would be the same as those obtained through the scoring of the case descriptions provided to the clinical experts.	High, favours asfotase alfa <i>rch</i>
Patient age	The model was highly dependent on the age that a patient starts treatment, with variations in the ICER of less than \$1 million per QALY gained for newborns and over \$3 million per QALY gained for paediatric onset HPP patients who initiate therapy as adults. The base case assumed that a patient would start treatment at the age of 5.8 years. The ICERs cannot be interpreted as a single cohort of patients where only the age of commencing treatment differs. The groups being modelled in each are distinct as the distribution of patients in each health state differs at "equivalent" ages across the analyses.	Uncertain as the proportion of patients likely to use asfotase alfa <i>rch</i> in different age groups is uncertain
Costs	The submission assumed that asfotase alfa <i>rch</i> would be self-administered. This may not be the case, due to the high cost of the medication and the need for medical supervision due to the potential for anaphylactoid/anaphylactic reactions. The submission did not include a cost for management of injection site reactions. The submission used ex-manufacturer costs rather than dispensed prices for asfotase alfa <i>rch</i> , which underestimated the overall cost. The submission also calculated the average annual direct medical [non-drug] cost for a patient aged 5 years or more to be \$1,124 for Severity level I versus \$90,963 for patients aged less than 5 years. It was not clear why there was such a big difference in the cost based on age group, especially considering that these costs did not include a cost for invasive ventilation.	Moderate, favours asfotase alfa <i>rch</i>

6MWT = six-minute walk test; BSC = best supportive care; AA = asfotase alfa *rch*

Source: compiled during the evaluation

Public Summary Document -July 2017 PBAC meeting

6.39 Results of the stepped economic evaluation are provided in Table 10.

Table 10: Results of the stepped economic evaluation, assuming age of initiation of treatment with asfotase alfa rch is 5.8 years

Step and component	Asfotase alfa rch	BSC	Increment
Step 1a (240-week data from Study ENB-006-09)			
Discounted drug cost	\$ [REDACTED]	\$0	\$ [REDACTED]
Mean change in 6MWT distance from baseline at 240 weeks (metres)	Not reported	Not reported	207.64
ICER: cost per additional metre walked			\$ [REDACTED]
Mean change in 6MWT distance from baseline as per cent of predicted, at 240 weeks (metres)	Not reported	Not reported	23.24
ICER: cost per additional metre walked as per cent of predicted			\$ [REDACTED]
Step 1b (192-week data from Trial ENB-009-10)			
Discounted drug cost	\$ [REDACTED]	\$0	\$ [REDACTED]
Mean change in 6MWT distance from baseline at 192 weeks (metres)	Not reported	Not reported	67.1
ICER: cost per additional metre walked			\$ [REDACTED]
Mean change in 6MWT distance from baseline as per cent of predicted, at 192 weeks (metres)	Not reported	Not reported	16.38
ICER: cost per additional metre walked as per cent of predicted			\$ [REDACTED]
Step 2 (drug cost only, CUA at 240 weeks)*			
Discounted drug cost	\$ [REDACTED]	\$0	\$ [REDACTED]
Discounted QALYs	3.02	1.82	1.20
ICER: cost per QALY gained			\$ [REDACTED]
Step 3 (drug cost only, CUA over a lifetime horizon for a patient starting treatment at 5.8 years)			
Discounted drug cost	\$ [REDACTED]	\$0	\$ [REDACTED]
Discounted QALYs	16.56	6.26	10.29
ICER: cost per QALY gained			\$ [REDACTED]
Step 4 (all costs, CUA over a lifetime horizon for a patient starting treatment at 5.8 years) – submission base case			
Discounted drug cost	\$ [REDACTED]	\$162,818	\$ [REDACTED]
Discounted QALYs	16.56	6.26	10.29
ICER: cost per QALY gained			\$ [REDACTED]

6MWT = six-minute walk test; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; CUA = cost-utility analysis; BSC = best supportive care

* Step 2 onwards follow on from Step 1a.

Source: Table D.5.10, pp69-70 of Sections C to F of the submission

6.40 The submission's approach of basing the first step of the economic evaluation on improvement in the 6MWT for asfotase alfa rch treated patients from baseline to Week 192 in ENB-009-10 (step 1b in Table 10) and from baseline to Week 240 in ENB-006-09 (step 1a in Table 10) did not include any allowance for the effect of a placebo or any comparison to indicate that the gain in 6MWT distance for asfotase alfa rch treated patients was statistically significant. In addition, in the only clinical evidence presented in relation to a control group comparison including the outcome of 6MWT (Trial ENB-009-10), the submission did not demonstrate an improvement in relation to change in 6MWT distance between the asfotase alfa rch and the untreated control groups. Overall, the ESC considered it was not possible to have confidence in the ICER per additional metre gained results presented in Table 10.

6.41 Moreover, the ESC considered that 6MWT may not be an acceptable surrogate outcome for paediatric-onset HPP, particularly for those aged less than 5 years where 6MWT was not (and could not be) assessed in any of the clinical trials. The ESC

Public Summary Document -July 2017 PBAC meeting

considered that 6MWT may not capture all the relevant clinical features of HPP such as skeleton and joint deformity and renal and neurological complications.

- 6.42 The base case ICER estimated in the submission was more than \$1 million per QALY gained. The base case ICER without the proposed risk share arrangement annual \$ [REDACTED] per patient cap was more than more than \$3 million per QALY gained.
- 6.43 For the base case, patients initiated treatment aged 5.8 years and there was no difference in mortality assumed between the treatment arms. The submission stated that generally more asfotase alfa *rch* treated patients remained in the less severe HPP health states over the time horizon in the model and that the lack of difference in mortality for the base case analysis was due to the assumption that HPP-related mortality was zero in patients initiating treatment with asfotase alfa *rch* aged 5 years and older.
- 6.44 The submission also provided age group specific ICERs (based on age of initiation of treatment with asfotase alfa *rch*). These are detailed in Table 11.

Table 11: Results of the modelled economic evaluation by age group at initiation of treatment with asfotase alfa *rch*

	Asfotase alfa <i>rch</i>	BSC	Incremental
Newborns, baseline age = 0 years			
Discounted total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Discounted total QALYs	15.16	1.72	13.44
ICER (cost per QALY gained)			\$ [REDACTED]
0-4 years, baseline age = 1.1 years			
Discounted total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Discounted total QALYs	15.64	3.50	12.14
ICER (cost per QALY gained)			\$ [REDACTED]
5-11 years, baseline age = 6.7 years			
Discounted total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Discounted total QALYs	16.51	6.22	10.30
ICER (cost per QALY gained)			\$ [REDACTED]
12-17 years, baseline age = 13.8 years			
Discounted total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Discounted total QALYs	16.26	6.69	9.57
ICER (cost per QALY gained)			\$ [REDACTED]
18+ years, baseline age = 51.6 years			
Discounted total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Discounted total QALYs	12.97	9.86	3.11
ICER (cost per QALY gained)			\$ [REDACTED]

Source: Table D.5.9, pp68-69 of Section C to F of the submission

- 6.45 The modelled economic evaluation was highly dependent on the age that patients started treatment, with an ICER of more than \$200,000 per QALY gained in patients commencing treatment as newborns, increasing to more than \$3 million per QALY gained in patients with paediatric-onset HPP who don't commence treatment with asfotase alfa *rch* until they are over 18 years of age. The ICERs could not be interpreted as representing a single cohort of patients where only the age of commencing treatment differs. The groups being modelled in each analysis are distinct, as the distribution of patients in each health state differs at "equivalent" ages across the analyses. The distinct groups may be partly justified in that perhaps only very severely affected patients are diagnosed as infants and only the "healthy"

patients survived to be included in clinical studies. Nevertheless, the ESC considered that there was a lack of clinical validity in the distributions of patients by age and severity level between the different analyses in Table 11 that may have resulted in an overestimation of the deterioration of patients in the BSC arm. For example:

- for the analysis of patients initiating treatment as newborns (aged 0) or when aged 0-4 years, almost 100% of patients are assumed to be in Severity level IV when aged 6 years; however, for the analysis of patients initiating treatment at 5.8 years (the base case), the distribution of patients is assumed to be 22%, 33%, 30% and 15% in Severity levels I-IV, respectively; and
- when patients initiated treatment at 5.8 years (the base case), as newborns (aged 0), or when aged 0-4, 5-11, 12-17 years, almost 100% of patients are assumed to be in Severity level IV when aged 52 years, however when initiating treatment at 51.6 years, the distribution of patients is assumed to be 30%, 35%, 25% and 10% in Severity levels I-IV, respectively.

6.46 The ICERs calculated by the submission were also considered to be highly uncertain for the following reasons:

- Movement between the alive health states in the model was based on comparisons of changes in observed/predicted 6MWT distance in patients treated with asfotase alfa *rch* from baseline rather than changes for asfotase alfa *rch* patients compared with a control group. Without a control group, the robustness of the efficacy data was limited. While the submission compared asfotase alfa *rch* to a historical control group, the comparative analyses were considered to be biased in favour of asfotase alfa *rch*. Movements between health states for patients treated with BSC were based on 12 transitions (out of a total of 34 comparisons of 6MWT health state at prior and current visit) observed over a short period of time. Thus, little confidence could be placed in the results, especially when they were modelled out to 101 years. An external validity check using health state traces showed that in the BSC arm more patients reached the most severe state than it is observed.
- The relationship between changes in 6MWT distance and changes in disease state severity was unclear including the fact that some symptoms experienced by patients with HPP, such as neurological complications, are not related to the endurance measured by the 6MWT.
- For patients aged less than 5 years, as changes in 6MWT distance were not assessed in any clinical trials, the degree of correlation between this outcome and changes in disease state severity were considered to be highly uncertain.
- There was uncertainty surrounding the utility gain from movement between health states because of the small number of health states, and the linking of the utility values to health state changes based on changes in 6MWT distance in the model rather than to a measure that encompassed all of the symptoms of HPP.
- The ICERs were highly dependent on the utility value for Severity level IV. With the high standard deviation of 0.25 for this utility value, and the lack of correlation between the case description used to derive the value and the HPP symptoms/complication rates for Severity level IV (see Table 12), little confidence could be put on the ICERs estimated by the submission.

- It was not clear that the threshold defining the difference in change in 6MWT distance between health states was appropriate, since despite indicating that the MCID was 8.8%, the submission presented an analysis using 8.9% in the economic evaluation, with this value being the MCID obtained from patients with Duchenne muscular dystrophy). The ICER was sensitive to changing the difference in 6MWT distance required for a patient to change to a different health state: assuming that only the MCID was required for movement to a different health state, rather than twice the MCID, increased the base case ICER to over \$1 million per QALY gained, and assuming three times the MCID was required for a patient to transition to a different health state increased the base case ICER to over \$1 million per QALY gained.
 - Uncertainty in the costs included in the model as the submission assumed:
 - self-administration, whereas the risk of anaphylaxis/anaphylactoid reactions highlighted that administration under medical supervision could be required;
 - that the same costs for direct medical care would apply to all patients aged under 5 years who weren't on invasive ventilation, and that these would be substantially higher than in patients aged 5 years or more regardless of severity level, which is unlikely; and
 - that patients who fail to improve would continue treatment.
- 6.47 To investigate some of the uncertainty surrounding the economic evaluation, the submission presented the results of univariate sensitivity analyses. The results of the sensitivity analyses for the base case for a patient starting treatment at the age of 5.8 years indicated that the model was most sensitive to the time horizon, with the ICER in a 10-year model increasing to over \$1 million per QALY gained.
- 6.48 The submission also presented univariate sensitivity analyses surrounding the results of the economic evaluation for patients initiating treatment as newborns and at 0-4 years of age. The model was most sensitive to changes in the utility values, with a constant utility of 0.24 for all children aged 5 years or less without invasive ventilation increasing the ICER by approximately four-fold (estimated at over \$3 million per QALY gained) in the newborn analysis and by approximately nine-fold (estimated at over \$5 million per QALY gained) in the 0-4 year analysis. As there was considerable uncertainty surrounding the model's approach of basing transitions in health states on change in 6MWT distance in patients aged less than 5 years, this sensitivity analysis was appropriate and indicated that if quality of life for these patients was constant, rather than based on any differential aspects of HPP severity, then the ICER was significantly higher.
- 6.49 In further sensitivity analyses undertaken during the evaluation for the newborn patient group, limiting the treatment duration to 2 years reduced the ICER to more than \$200,000 per QALY gained. Assuming a constant utility of 0.24 for all children aged 5 years and less for the same newborn treatment group, with a treatment duration of 2 years, increased the ICER to more than \$ 1 million per QALY gained.
- 6.50 Given the similarity of symptoms and complications between Severity levels III and IV (see Table 12), a sensitivity analysis was also undertaken during the evaluation, which

Public Summary Document -July 2017 PBAC meeting

assumed the same utility value for Severity level IV as for Severity level III and this increased the ICER to over \$2 million per QALY. As the base case for the model assumed no difference in the number of life years saved, the ICER was based entirely on the submission’s claim of improvements to quality of life. Therefore the health state specifications used and the utility values assigned to those health states were critical to the ICER.

Table 12: HPP symptom/complication prevalence in patients in each severity level in the model

HPP symptom/complication	Severity level I % (n/N)	Severity level II % (n/N)	Severity level III % (n/N)	Severity level IV % (n/N)
Respiratory compromise (no ventilation)	-	50% (3/6)	59% (13/22)	50% (3/6)
Nausea, vomiting, difficulty to eat; failure to thrive	-	67% (4/6)	50% (27/54)	34% (13/38)
Bone malformation and fractures	-	33% (2/6)	10% (9/87)	9% (6/70)
Renal compromise	-	33% (2/6)	10% (9/87)	9% (6/70)
Growth impairment and delay	-	17% (1/6)	72% (62/86)	71% (50/70)
Seizure	-	50% (3/6)	9% (5/54)	5% (2/38)
Bone/joint/muscle pain	-	100% (6/6)	71% (62/87)	64% (45/70)
Dental problems	94% (66/70)	94% (66/70)	93% (80/86)	91% (64/70)

Severity level I = 6MWT score > 82.2% of predicted value; Severity level II = 82.2% ≥ 6MWT score > 64.4% of predicted value; Severity level III = 64.4% ≥ 6MWT score > 46.6% of predicted value; Severity level IV = 6MWT score ≤ 46.6% of predicted value. For patients aged <5 years (for whom the 6MWT score is not relevant) relative disease severities between Severity levels are the same as for patients aged ≥5 years

Source: Table C.6.3, pp38-39 of Sections C to F of the submission

Drug cost/patient/year

Table 13: Drug cost per patient per year by age

Age (years) Range ^a	Average patient weight (kg) ^a	mg/dose ^b	Vial strength dispensed (mg)	Vials/ week	Total mg dispensed/year	Cost ^c	
						With cap	Without cap
0-1	5.3	10.6	18	3	2,808	\$ [REDACTED]	\$ [REDACTED]
1-4	12.5	25.0	28	3	4,368	\$ [REDACTED]	\$ [REDACTED]
5-11	22.0	22.0	28	6	8,736	\$ [REDACTED]	\$ [REDACTED]
12-17	45.0	45.0	80	6	24,960	\$ [REDACTED]	\$ [REDACTED]
18+	71.0	71.0	80	6	24,960	\$ [REDACTED]	\$ [REDACTED]

^a according to age ranges and mean weights reported on 'Cost of drug to PBS' worksheet in Asfotase_alfa_Section E.xls

^b based on 6mg/kg/week and dosing at 2mg/kg 3 times per week for those aged ≤4 years and 1mg/kg 6 times per week for those aged >4 years

^c without cap = \$ [REDACTED] (requested ex-manufacturer price)

Estimated PBS usage & financial implications

6.51 This submission was not considered by DUSC. The submission followed an epidemiological approach to estimate the number of patients with paediatric-onset HPP in Australia over the analysis period of 2018 to 2022. As there was limited published data, the submission used its experience in ultra-rare diseases to estimate prevalence rates by age group. The submission’s prevalence based approach did not appear to have included an allowance for improved survival in newborns and infants, even though the submission expected that asfotase alfa *rch* would improve survival in patients with perinatal/infantile-onset HPP. The estimated use and financial implications of listing asfotase alfa *rch* on the PBS is summarised in Table 14.

Public Summary Document -July 2017 PBAC meeting

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Total number of patients treated	█	█	█	█	█
- 0-<1 year	█	█	█	█	█
- 1-4 years	█	█	█	█	█
- 5-11 years	█	█	█	█	█
- 12-17 years	█	█	█	█	█
- 18+ years	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█
Number of packs supplied per year ^b	█	█	█	█	█
Estimated financial implications of asfotase alfa <i>rch</i> (with annual patient cap of \$ █ per patient per year)					
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █
Co-payments	\$ █	\$ █	\$ █	\$ █	\$ █
Cost to PBS/RPBS less co-payments	\$ █	\$ █	\$ █	\$ █	\$ █
Net financial implications					
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to PBS/RPBS/MBS	\$ █	\$ █	\$ █	\$ █	\$ █

^a Assuming patients are dispensed only the one strength vial, with the number of vials per script being based on average body weight for each age group from trial data as estimated by the submission.

^b In some cases the submission calculated that two packs would be required per prescription

Source: Tables E.2.2 – E.5.2, pp79- 88 of Sections C to F of the submission

6.52 At year 5, the submission estimated the number of patients would be less than 100 and the net cost to the PBS would be \$20 - \$30 million in Year 5 of listing. This cost may be higher due to:

- Uncertainty in the eligible population because the prevalence population may be higher than estimated, the diagnosis and uptake rates may be different to that estimated by the submission, there could be variation in the proportion of patients in each age group compared with what is reported in the submission, and there could be use outside the restriction in adult patients, where quantification of symptom onset prior to 18 years of age as proposed by the submission is subjective.
- Uncertainty in the costs since the submission assumed self-administration, whereas administration under medical supervision may be required due to the risk of anaphylactoid/anaphylaxis reactions, and also because the submission did not include any cost for the treatment of such reactions.
- Uncertainty in the costs since the submission assumed average body weight to be the same as average body weight in the trials.

6.53 The PBAC noted that the submission assumes that, overall, only around █% of the estimated eligible patient population with paediatric-onset HPP will be treated. Table 15 provides the submission estimates of the eligible patient population.

Table 15: Estimation of the number of eligible patients with paediatric HPP

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
0-1< year					
1-4 years					
5-11 years					
12- 17 years					
18+ years					
Total					

Number of patients rounded to whole numbers, but the exact percentages based on prevalence calculations were used in all the calculations in the submission

Source: Table E.2.1, pp78-79 of Sections C to F of the submission

6.54 The above table of shows the submission estimated that at year 5, the total number of patients eligible for asfotase alfa was less than 1,000.

6.55 In a sensitivity analysis undertaken during the evaluation (Table 16), should the diagnosis and treatment rates for patients with paediatric-onset HPP who are aged over 18 years be the same as the rates for patients aged 12-17 years, the estimated cost to the PBS/RPBS/MBS would increase to \$60 - \$100 million in Year 5 of listing, a greater than 3-fold increase on the submission's estimates.

Table 16: Sensitivity analysis on financial estimates

		Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Base case (with annual cap)		\$	\$	\$	\$	\$
Sensitivity analyses (with annual cap)						
Prevalence rates for the 1-17 and 18 + years age groups	Increased by 50% to 9.6 cases per million	\$	\$	\$	\$	\$
	Decreased by 50% to 3.2 cases per million	\$	\$	\$	\$	\$
Diagnosis rates for paediatric-onset HPP	Decreased by 50%	\$	\$	\$	\$	\$
Treatment rates for paediatric-onset HPP	Decreased by 50%	\$	\$	\$	\$	\$
<i>Diagnosis and treatment rate in patients 18 years and over</i>	<i>Same as diagnosis and treatment rate in patients aged 12-17 years</i>	\$	\$	\$	\$	\$

Figures in italics calculated during the evaluation

Source: Table E.6.1, p88 of the Sections C to F of the submission

6.56 The PBAC further noted that if treatment were extended to include patients diagnosed with adult-onset HPP, the total patient population is likely to be further increased.

Quality Use of Medicines

6.57 The submission proposed to develop a Patient Support Program to ensure that patients would receive access to training on self-administration, consistent information about their treatment, and ongoing support in the home when establishing a treatment schedule. The evaluation considered it may not be appropriate for patients to self-administer asfotase alfa *rch* due to some potential for risk of wastage from breakages and a risk of anaphylactoid/anaphylactic reactions.

6.58 The PSCR (p4) stated asfotase alfa *rch* has been successfully self-administered by over 300 patients and their carers through Alexion's patient support programs. The sponsor

claims anaphylactoid reactions/anaphylaxis can be managed in the home and self-administration is the most practical way to adhere to the 3 or 6 injections per week. The ESC considered this claim was uncertain and also raised that incorrect self-administration procedures may result in drug wastage or inadequate dosing.

Financial Management – Risk Sharing Arrangements

- 6.59 To ensure equity of access to all patients based on their disease severity rather than their body weight, the submission proposed a Risk Share Arrangement (RSA) with an annual per patient cap of \$██████ per year. The financial estimates and the economic evaluation provided in the submission contained this cap.
- 6.60 In addition to a per patient cap, the evaluation noted that an overall financial cap may also be appropriate given the uncertainties surrounding (i) the eligible population; (ii) diagnosis and uptake rates; (iii) variations in the ages (and weights) of patients who are likely to be treated; and (iv) the potential for use beyond the restriction with the subjective requirements for establishing paediatric-onset HPP. The PSCR (p4) stated that the sponsor would be willing to negotiate an overall financial cap, in addition to the proposed per patient cap.

For more detail on PBAC's view, see section 7 "PBAC outcome."

7 PBAC Outcome

- 7.1 The PBAC did not recommend the requested Section 100 (Highly Specialised Drugs Program) listing of asfotase alfa *rch* for the treatment of patients with paediatric-onset HPP. The PBAC accepted that there is likely to be a survival benefit associated with treatment with asfotase alfa *rch* for children with perinatal- or infantile-onset (i.e. up to 6 months of age) HPP who were at high risk of premature death (as defined by the presence of respiratory compromise, vitamin B6 responsive seizures and/or rachitic chest deformity). However, the PBAC considered that the claim of superior comparative effectiveness in the broader paediatric-onset population (i.e. up to 18 years of age) was not adequately supported by the submission. The PBAC considered that the submission presented a high and very uncertain ICER, especially in the group of patients in whom no benefit of life extension is claimed (in those other than the perinatal and infantile types). The PBAC also considered there was substantial uncertainty around the size of the patient population and financial estimates, and that both were likely to be considerably higher than estimated by the submission, again mostly due the milder forms of the disease where a population prevalence of 1:6000 may be possible.
- 7.2 The PBAC acknowledged the consumer comments received, both from people living with the condition and on behalf of patients and their carers. In addition, representatives of the PBAC met with Soft Bones Australia prior to the PBAC meeting to discuss the clinical place and potential benefits of asfotase alfa *rch* for the requested patient population. The PBAC noted that the consumer comments indicated that subsidised access to asfotase alfa *rch* would be preferred for all forms of

HPP, as opposed to just the requested population of paediatric-onset (although TGA approval is currently limited to paediatric-onset HPP).

- 7.3 The PBAC recognised the potential clinical value of asfotase alfa *rch* in the treatment of HPP which is a rare genetic disease resulting from decreased enzymatic activity of TNSALP and presents with significant heterogeneity in morbidity and mortality. The PBAC noted that while HPP is a genetic condition, symptoms such as skeletal deformity, chronic pain, muscle weakness and rickets can appear at any time from before birth to adulthood. The most severe form of disease presents in infants up to 6 months of age (perinatal- and infantile-onset), with increased risk of mortality resulting from respiratory failure.
- 7.4 The PBAC noted that diagnosis is based on family background, symptoms and blood test results and can be confirmed with genetic testing (which can take several months). The PBAC noted the potential difficulty in diagnosing the condition, especially the milder forms, due to the rarity of the disease and the range of symptoms that may present at various ages. Accordingly, the PBAC noted that age of onset will not necessarily be the same as the age at diagnosis; many patients diagnosed as adults may have a history of symptoms throughout childhood and could potentially meet the criteria for subsidised treatment in the requested listing. The PBAC considered the requested listing was complex and consultation with rare diseases experts would be required to develop a suitable restriction for the PBS.
- 7.5 The submission nominated BSC as the main comparator. The PBAC considered that this was appropriate.
- 7.6 The PBAC noted that the submission was based on one head-to-head randomised trial comparing asfotase alfa *rch* (n=13) with best supportive care (n=6), five supplementary non-randomised studies and a retrospective epidemiological review of patients receiving BSC.
- 7.7 The submission presented the results of a survival analysis from three of the supplementary non-randomised studies in patients with perinatal- and infantile-onset HPP who were at high risk of premature death (as defined by the presence of respiratory compromise, vitamin B6 responsive seizures and/or rachitic chest deformity), compared with a matched control group from the retrospective epidemiological review of patients receiving BSC. Specifically, the submission showed:
- A death rate of 8.8% (6/68) for patients in the asfotase alfa *rch* group compared to 72.9% (35/48) in an untreated historical control group during the time period of evaluation ($p \leq 0.0001$).
 - Comparative death rates of █% (█) versus █% (█) ($p = \text{█}$) in a sensitivity analysis that adjusted the data to only include historical control patients diagnosed after the year 2000.
 - Comparative death rates █ between asfotase alfa treated patients and historical control patients were statistically significant in favour of asfotase alfa treatment ($p = \text{█}$), in a sensitivity analysis that only included historical control patients who survived to █ weeks.

- 7.8 On this basis, the PBAC considered there was likely to be a survival advantage associated with treatment with asfotase alfa *rch* in patients with perinatal- and infantile-onset HPP who were at high risk of premature death. However, the PBAC considered that the magnitude of the survival benefit was unclear given the matched analysis was associated with a high risk of bias. Additionally, the PBAC noted that the persistence of any survival benefits of asfotase alfa *rch* were uncertain, even in this group.
- 7.9 The PBAC also noted that the pre-PBAC response stated that a survival benefit for asfotase alfa *rch* in patients with juvenile-onset (6 months to 17 years) HPP was not evaluated in the submission as the clinical manifestations in this cohort do not cause short-term mortality.
- 7.10 The PBAC noted there was a significant difference in relation to the primary outcome in the randomised trial of a reduction in PPI and PLP levels (from baseline to 24 weeks). However, the PBAC considered that it was unclear what magnitude of change in PPI and PLP would be clinically meaningful for patients. The PBAC further noted that no statistically significant differences in improvement in 6MWT distance or quality of life were observed in the randomised trial. Accordingly, the PBAC considered that an improvement in morbidity for patients with juvenile-onset HPP was not supported by the submission.
- 7.11 The PBAC noted the base case ICER presented in the submission (which included the impact of the proposed annual per patient cap of \$ [REDACTED] per year) was unacceptably high at more than \$1 million per QALY gained. In the base case, patients began treatment at 5.8 years and there was no overall survival benefit associated with treatment with asfotase alfa *rch*. The PBAC noted that the submission presented ICERs by age of initiation of treatment which ranged from more than \$200,000 per QALY gained for newborns to over \$3 million per QALY gained for adults. The PBAC considered that the ICERs presented in the submission were highly uncertain due to the following issues with the economic model:
- The economic model was based on the outcome of changes in the 6MWT, overall survival and invasive ventilator-free survival and was therefore reliant on secondary outcomes with non-significant changes or post-hoc analyses.
 - The model structure lacked clinical validity. The four alive health states in the model (Severity levels I-IV) were based on per cent predicted distance on the 6MWT. The PBAC considered that 6MWT does not adequately capture all the effects of treatment on the various body systems affected by the disease (e.g., skeleton and joint deformity and renal and neurological complications), and was therefore a poor surrogate for disease state severity for patients with paediatric-onset HPP. This was particularly the case for those aged less than 5 years where 6MWT was not assessed in any of the clinical trials.
 - Movements between health states for patients treated with BSC were based on a small number of transitions observed over a short period of time. Thus, little confidence could be placed in the results, especially when they were modelled out to 101 years.

Public Summary Document -July 2017 PBAC meeting

- The utilities for each of the alive health states in the model (based on change in 6MWT distance), were uncertain as they were derived from clinical experts based on information describing patients with a wide range of symptoms. There was a lack of correlation between the case descriptions and the HPP symptoms/complication rates associated with those descriptions.
 - The costs included in the model were uncertain as the submission assumed self-administration, that the same costs for direct medical care would apply to all patients under 5 years who weren't on invasive ventilation, and that these costs would be substantially higher than in patients aged 5 years or more regardless of severity level.
- 7.12 The PBAC considered the cost to the PBS may be higher than estimated in the submission due to multiple uncertainties in the submission, including disease prevalence, definitive diagnosis, treatment of older patients, weight based dosing, drug administration and use outside the proposed paediatric-onset restriction. In this regard, the PBAC considered that a tight subsidisation cap through an RSA would be important if asfotase alfa *rch* were recommended for listing.
- 7.13 The PBAC noted the submission's request that, if rejected by the PBAC for PBS listing, consideration be given to including asfotase alfa *rch* on the Life Saving Drugs Program (LSDP) for paediatric onset HPP. The PBAC further noted that the Commonwealth Chief Medical Officer (CMO) advises the Minister on drugs proposed to be included on the LSDP.
- 7.14 The PBAC advised the CMO that if asfotase alfa *rch* were to be considered for inclusion on the LSDP, the following outcomes from the PBAC's review may be relevant:
- any survival advantage associated with treatment with asfotase alfa *rch* is limited to patients with perinatal- and infantile-onset HPP who are at high risk of premature death (as per the definition above);
 - the magnitude of the survival benefit was unclear given the matched analysis was associated with a high risk of bias;
 - the persistence of survival gains with asfotase alfa *rch* in this severe patient group beyond 5 years is uncertain and further evidence will be required to support ongoing use beyond 5 years of age in this population; and
 - asfotase alfa *rch* is not cost-effective in the perinatal- and infantile-onset population at the proposed price.
- 7.15 The PBAC further considered that the PBS may be the most appropriate mechanism for subsidising treatments for juvenile onset HPP and, noting the patient communities preference for access to subsidised treatment for all patients with HPP, also for adult onset HPP. This is because:
- juvenile- and adult-onset disease appears to be associated with quite different morbidity and mortality to perinatal- and infantile-onset HPP;

- the aims of treatment in the two patient groups appear to be quite different;
- the size of the juvenile- and adult-onset patient population who would likely seek treatment through the PBS is comparable to other conditions with PBS subsidised treatments, and very large compared to most LSDP funded conditions; and
- whilst a number of genetic conditions resulting in enzyme deficiencies currently have treatments subsidised through the LSDP, pharmacological treatments for other genetic conditions, including cystic fibrosis, are subsidised through the PBS.

7.16 The PBAC considered that if the sponsor wishes to pursue PBS listing for juvenile- and adult-onset HPP, a major resubmission would need to establish both the clinical and cost effectiveness of treatment with afotase alfa *rch* compared with best supportive care. The sponsor may wish to identify a more specific patient population in which cost-effectiveness might be improved compared with the current submission's proposed patient population. However, the PBAC considered that even in a more specific patient population, a substantial price reduction would likely be required for asfotase alfa *rch* to be considered to be suitably cost-effective to enable a recommendation for listing on the PBS.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Alexion is actively seeking an expedited LSDP listing for all patients with Perinatal/Infantile-Onset HPP to ensure timely access for asfotase alfa *rch*.

Juvenile-onset HPP is also an ultra-rare disease associated with significant disease burden severely affecting patients' quality of life as highlighted by the patient representatives and reflected in the published evidence. Alexion intends to work with the Dept. of Health to explore appropriate ways to secure access for patients with juvenile-onset HPP.