7.01 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 resubmission requested a Section 100 (Highly Specialised Drugs Program), Authority Required PBS listing for asfotase alfa *rch* in the treatment of patients with juvenile-onset hypophosphatasia (HPP; onset between the ages of 6 months and 17 years), on the basis of 'rule of rescue'. This compared to a requested listing for paediatric HPP (including perinatal- [onset before or at birth], infantile- [onset 0-6 months] and juvenile- onset HPP) in the previous submission.

1.2 This was the second submission for PBS listing. The first submission was considered at the July 2017 PBAC meeting.

1.3 The resubmission requested listing on the basis of a cost-utility analysis compared to best supportive care. The key components of the clinical issue addressed by the resubmission are presented in Table 1.

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

Component	Description
Population	Patients with juvenile-onset HPP [onset between 6 months and 17 years]
Intervention	Asfotase alfa rch 6mg/kg/week via subcutaneous injection, better described as asfotase alfa rch used in combination with best supportive care (BSC)
Comparator	Best supportive care (BSC); better described as BSC alone. The PBAC has previously accepted that BSC is the appropriate comparator (Paragraph 7.5; Asfotase alfa rch PSD, July 2017).
Outcomes	Six-minute walk test (6MWT): relied upon for the economic model. Other outcomes included Radiographic global impression of change (RGI-C), Rickets severity score (RSS), and reduction in plasma PPi and PLP levels
Clinical claim	Asfotase alfa rch is superior in terms of comparative effectiveness and non-inferior in terms of comparative safety to best supportive care (requires consideration, see below for discussion).

HPP = Hypophosphatasia; PLP = pyridoxal 5-phosphate; PPi = inorganic pyrophosphate
Source: Compiled during the evaluation from Sections 1 and 2 of the resubmission.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (units)	№.of Rpts	Dispensed Price for Max. Qty[a]		Proprietary Name and Manufacturer	
			Public	*Private*		
ASFOTASE ALFA *RCH*					Strensiq®	XI
Injection 18 mg in 0.45 mL,	12	TBD	$[redacted]	$[redacted]		
vial	12	TBD	$[redacted]	$[redacted]		
Injection 28 mg in 0.7 mL, vial	12	TBD	$[redacted]	$[redacted]		
Injection 40 mg in 1 mL, vial	12	TBD	$[redacted]	$[redacted]		
Injection 80 mg in 0.8 mL, vial						

[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.
TBD = to be determined: the previous submission requested 0 repeats

Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Juvenile-onset Hypophosphatasia (HPP)
Treatment phase:	Initial treatment
Restriction:	Authority required – in writing
Treatment criteria:	All infants aged between 6 and 12 months with juvenile-onset HPP, confirmed by age- and gender-adjusted alkaline phosphatase (ALP) activity below lower limit of normal and by the presence of HPP-related bone disease (by skeletal imaging), should be treated immediately. *OR* Patients with ALP activity *below* lower limit of age- and gender-adjusted normal range *AND* Patients with non-HPP-related causes of low ALP are excluded *OR* Confirmed by Mutational Analysis *AND* Patients with available childhood medical records documenting HPP-related symptoms after 6 months and before 18 years of age, consistent with juvenile-onset disease *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: Respiratory compromise requiring mechanical ventilation or oxygen supplementation within the last 12 months OR Failure to thrive, defined as a reduction in the z-score for weight for length of 1 SD or greater within the last 12 months OR Vitamin B6-dependent seizures within the last 12 months OR Developmental delay; missed developmental milestones, relative to a normative sample, as defined by a validated scale within the last 12 months OR History of two or more non-traumatic, non-/poorly healing fractures requiring surgical fixation PLUS currently presenting with: Severely impaired mobility, relative to a normative sample, as defined by a validated scale, due to HPP-related skeletal deformities requiring assistance devices or home modification AND Chronic muscular/joint and/or bone pain severe enough to limit the performance of activities of daily living/functional independence, as defined by a validated scale, requiring prescription pain medication.
Clinical criteria:	Continuing treatment
Population criteria:	Authority required in writing
Prescriber criteria:	Evidence of clinical improvement or stabilisation of the patient's condition to support ongoing eligibility for asfotase alfa *rch* treatment*
Clinical criteria:	Recommencement of treatment
Population criteria:	Authority required in writing
Prescriber criteria:	Patient must have discontinued PBS-subsidised asfotase alfa *rch* AND

	Patient must have experienced clinical deterioration based on 1 or more of the assessment scales, relative to the patient's last on treatment evaluation

* 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 resubmission proposed a price per mg of $[redacted] (this compared with $[redacted]/mg in the previous submission) and an annual expenditure cap through a risk sharing arrangement of $[redacted] per patient per year (this compared with a patient cap of $[redacted]/patient/year in the previous submission). The ESC noted the resubmission also proposed an overall spending cap.

2.2 Compared to the previous submission, the resubmission did not request PBS listing for patients with onset of HPP before 6 months of age, stating that eligible patients with perinatal/infantile-onset HPP (age of onset 0 to less than 6 months) will be considered for a subsidy through the life-saving drugs program (LSDP).

2.3 As for the previous submission, the restriction will require development in consultation with rare diseases experts. The ESC advised that the current proposed restriction is complex and, whilst it does narrow the eligible population, it would likely require further modification. In particular, genetic testing for the relevant mutations in the Alkaline Phosphatase, Liver/Bone/Kidney (ALPL) gene that can cause this condition may be required. The ESC advised the proposed restriction allows adults who report HPP symptoms in infancy or childhood to access subsidy and that this may not be a reliable means to determine eligibility and that this introduces considerable uncertainty in the estimated eligible population and hence the cost effectiveness. The pre-PBAC response stated that eligibility criteria should be based on severity of the patients' presenting symptoms and not on their age at the time of evaluation for PBS eligibility. The PBAC considered the heterogeneity of the population who would be eligible under this proposal also contributes significantly to the uncertainty of the magnitude of benefit claimed in the submission.

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).

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

3 Background

Registration status

3.1 Asfotase alfa rch was TGA registered on 14 January 2016 as enzyme replacement therapy in patients with paediatric-onset HPP.

Previous PBAC consideration

3.2 The first submission was considered by the PBAC in July 2017. Table 2 summarises the outstanding matters of concern and how the resubmission addresses them.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical effectiveness	A claim of superior comparative effectiveness was not adequately supported in the population with onset of symptoms from 6 months to 18 months of age (Para 7.1). No statistically significant differences in improvement in 6MWT distance or quality of life in ENB-009-10 (Para 7.10). Improvement in morbidity for patients with juvenile-onset HPP was not supported (Para 7.10)	Not addressed; same trial and study presented
Prevalence of the disease	The patient population and financial estimates are likely to be higher than estimated, mostly due to milder forms of the disease where a population prevalence of 1:6000 may be possible (Para 7.1)	[redacted]; same prevalence assumed
Economic model	Reliant on secondary outcomes with non-significant changes or post-hoc analyses and movement between health states reliant on a small number of transitions over a short-period of time (Para 7.11)	Not addressed; the economic model did not change in relation to its reliance on a secondary outcome and being based on a small number of transitions observed over a short period of time
	Utilities uncertain as derived from clinical experts based on information describing patients with a wide range of symptoms. Lack of correlation between the case descriptions and the HPP symptoms/complications associated with those descriptions (Para 7.11)	Not addressed: utilities the same (although updated scoring of EQ-5D-5L) and based on same case descriptions
	Uncertain costs due to assumption of self-administration (Para 7.11)	Not addressed: self-administration assumed
	Uncertain costs due to assumption of same costs for direct medical care for all patients under 5 years not on invasive ventilation (Para 7.11)	Assumption that costs for patients under 5 years will be the same as for all patients: no justification provided
Risk share arrangement	Cost to the PBS may be substantially higher and a tight subsidisation cap through a risk share arrangement would be important: an overall financial cap may be appropriate in addition to a per patient cap (Para 7.11 and 6.60)	Patient cap proposed; Overall financial cap proposed to year 6
Patient population	Identification of a more specific population in which cost-effectiveness might be improved (Para 7.16)	Not addressed: All remaining patients outside of onset of HPP from 0-6 months of age were requested in the proposed listing
Price	Even in a more specific patient population, a substantial price reduction would likely be required (Para 7.16)	A reduction in price from $[redacted] per mg to $[redacted] and a reduced annual cap per patient from $[redacted] to $[redacted]. Annual expenditure cap based on per patient cap and the uptake estimates in the submission.

Para = paragraph; HPP = Hypophosphatasia; 6MWT = six-minute walk test
Note: All paragraph references refer to the Asfotase alfa *rch* PSD, July 2017 unless otherwise stated
Source: Compiled during the evaluation.

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

4 Population and disease

4.1 Hypophosphatasia (HPP) is a rare disease. The disease presents as a continuum, with significant heterogeneity in clinical manifestations, 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].

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 patients with juvenile-onset HPP patients can present with symptoms such as delayed growth, rickets like bone disease, limitations in movement, fatigue, loss of teeth as well as osteomalacia, kidney stones, raised intracranial pressure from premature craniosynostosis, nephrocalcinosis and pyridoxine-responsive seizures.

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.

Asfotase alfa rch would be used in addition to best supportive care.

5 Comparator

5.1 The resubmission nominated best supportive care (BSC) as the comparator, better described as BSC alone, on the basis that there are no other therapeutic options that treat the underlying cause of HPP. In its consideration of the July 2017 submission, the PBAC accepted that BSC was the appropriate comparator (Paragraph 7.5; Asfotase alfa rch PSD, July 2017).

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 functional impairment of children and adolescents with HPP along with a brief overview of the clinical trial data. The presentation highlighted the benefits of asfotase alfa *rch* in assisting with mobility and improved quality of life, whilst noting the difficulties in obtaining data from randomised clinical trials (RCTs) in rare genetic diseases. The clinician suggested a homogenous treatment effect was

expected despite age of treatment initiation and that discontinuations could be attributed to adverse events. The PBAC considered that, given the magnitude and consistency of the treatment effect expected, RCTs should be able to demonstrate a clinically significant benefit with only small numbers and that perceived lack of power should not necessarily be an issue. The PBAC considered the hearing was informative as it provided a clinical perspective on treating this rare disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (55), health care professionals (3) and an organisation (3) 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 reduced pain, reduced disability, delayed disease progression, less fatigue and increased mobility and bone strength.

6.3 The PBAC noted the advice received from Soft Bones Australia, Soft Bones Canada and Soft Bones USA that considered asfotase alfa *rch* to be an important medicine in the symptomatic control of HPP. The comments noted the main symptoms reported from HPP patients are pain and fatigue. In particular, it was that noted pain appeared to have the largest effect on mobility. The comments indicated that subsidised access to asfotase alfa *rch* would be beneficial for older patients in addition to infantile onset.

Clinical trials

6.4 The resubmission was based on one head-to-head trial comparing asfotase alfa *rch* to BSC (n=19) ENB-009-10, and two supplementary single arm open-label studies: ENB-006-09 and extension study ENB-008-10 (n=13), referred to as Study ENB-006-09/ENB-008-10 herein; and data from a historical control group of patients with infantile or juvenile-onset HPP matched to patients from ENB-006-09/ENB-008-10 (Shriner's HPP). Both Trial ENB-009-10 and Study ENB-006-09/ENB-008-10 enrolled patients with infantile- or juvenile- onset HPP.

6.5 The resubmission also presented data on a sponsored non-interventional natural history study (ALX-HPP-502 and a substudy of ALX-HPP-502).

6.6 As the resubmission was requesting listing in juvenile-onset HPP only, the resubmission additionally provided analyses of the subgroup of patients with juvenile-onset HPP (n=8) from Study ENB-006-09/ENB-008-10 for the primary outcome of radiographic global impression of change (RGI-C) and Rickets severity score (RSS, secondary outcome), both compared to historical controls; and the six minute walk test (6MWT), with no comparison to a control group; to inform its clinical claim in juvenile-onset patients.

6.7 All trials and studies were presented in the previous submission. The resubmission reasonably excluded the ENB-002-08 study and extension study ENB-003-08 and studies ENB-010-10 and ENB-011-10 (presented in the previous submission), since these studies did not include any patients with juvenile-onset HPP.

6.8 Details of the trials and associated reports presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

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).	2 April 2015
	Kishnani PS, Madson KL, Whyte MP, *et al*. 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.	1-4 April 2016[98th] Annual Meeting of the Endocrine Society (ENDO); Boston, MA. Abstract 25979. Presentation OR26-3
	Kishnani PS, Rockman-Greenberg C, Whyte M, *et al*. Enzyme replacement therapy (ENB-0040) decreases TNSALP accumulation and improves functional outcome in affected adolescents and adults.	*Molecular Genetics and Metabolism* 2012;105(3):328-329
	Whyte MP, Rockman-Greenberg C, Ozono K, *et al*. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia.	*J Clin Endocrinol Metab 2016;101:334-42*
	Kishnani, P., Gayron, M., Denker, A., Watsky, E. & Rockman-Greenberg, C. Biochemical and physical function outcomes in adults with pediatric-onset hypophosphatasia treated with asfotase alfa for up to 3 years: interim results from a Phase 2 study.	21-24 August 2016 *The Joint Annual Scientific Meeting of Endocrine Society of Australia & the Society for Reproductive Biology & ANZ Bone & Mineral Society. Queensland, AUS*
	Kishnani, P. S., Rockman-Greenberg, C., Denker, A. E., Moseley, S. & Whyte, M. P. Biochemical and physical function outcomes in adolescents and adults with hypophosphatasia treated with asfotase alfa for 5 years: Results from a phase 2 study.	*Calcif. Tissue Int.* **100 (1 Sup,** S134–S135 (2017).
	Tomazos, L. C., Moseley, S., L'Italien, G., Da Silva, H. G. & Phillips, D. Improvements in the 6-minute walk test and correlation with quality-of-life measures in children and adults with hypophosphatasia treated with asfotase alfa.	*Endocr. Rev. Conf. 99th Annu. Meet. Endocr. Soc. ENDO* **38,** (2017).
Single arms of open-label studies with asfotase alfa *rch*		
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).	3 April 2015
	Whyte MP, Madson K, Phillips D, *et al*. Asfotase alfa therapy for children with hypophosphatasia.	*JCI Insight* 2016:1(9):e85971
	Tomazos, L. C., Moseley, S., L'Italien, G., Da Silva, H. G. & Phillips, D. Improvements in the 6-minute walk test and correlation with quality-of-life measures in children and adults with hypophosphatasia treated with asfotase alfa.	*Endocr. Rev. Conf. 99th Annu. Meet. Endocr. Soc. ENDO* **38,** (2017).
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).	3 April 2015
	Whyte MP, Madson K, Phillips D, *et al*. Asfotase alfa therapy for children with hypophosphatasia.	*JCI Insight* 2016:1(9):e85971
	Tomazos, L. C., Moseley, S., L'Italien, G., Da Silva, H. G. & Phillips, D. Improvements in the 6-minute walk test and correlation with quality-of-life measures in children and adults with hypophosphatasia treated with	*Endocr. Rev. Conf. 99th Annu. Meet. Endocr. Soc. ENDO* **38,** (2017).

	asfotase alfa.	
Historical control studies		
ALX-HPP-502	Whyte MP, Madson KL, Munns CF, Reeves AL, Fujita KP, Zhang H and Bishop NJ. A retrospective, multinational, non-interventional, natural history study of the childhood form of hypophosphatasia. Radke J. ENDO 2015: Hypophosphatasia in the Spotlight. Rare Disease Report.	*5 March 2015* *Abstract LB-OR01-4* *9 March 2015* *ENDO 2015 (published online at http://www.raredr.com/articles/ENDO-2015-Hypophosphatasia)*
ALX-HPP-502 substudy	Phillips D, Griffin D, Przybylski T, Morrison E, Reeves AL, Vallee M, Fujita KP, Madson KL, and Whyte MP. Gait assessment in children with childhood Hypophosphatasia. Radke J. ENDO 2015: Hypophosphatasia in the Spotlight. Rare Disease Report.	*5 March 2015* *Abstract LB-039* *9 March 2015* *ENDO 2015 (published online at http://www.raredr.com/articles/ENDO-2015-Hypophosphatasia)*

6.9 The key features of the included trial and studies are summarised in Table 4.

Table 4: Key features of the included evidence; asfotase alfa rch vs. best supportive care

Trial	N	Treatment arms	Trial design	Primary outcome	Use in the economic evaluation
Direct randomised trials					
ENB-009-10	13 6	Asfotase alfa *rch* Concurrent control group*	OL, R*	• 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
Single-arm open-label studies with asfotase alfa *rch*					
ENB-006-09	13** 16	Asfotase alfa *rch* Historical control group***	OL	• Effect of AA in treating HPP-related rickets (RGI-C) 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				• 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	
Historical control studies					
ALX-HPP-502	32	Best supportive care	RR	• 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		RR	• Gait performance evaluated from recorded video measured by the MPOMA-G	Not used

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

** 8 with juvenile-onset HPP

*** Shriner's HPP Matched historical control group of 16 patients

OL=open-label; R=randomised; RR = retrospective review: 6MWT = six-minute walk test; AA = asfotase alfa *rch*: HPP = Hypophosphatasia; SC = subcutaneous; RGI-C = radiographic global impression of change; MPOMA-G = modified performance-oriented mobility assessment;

Source: Compiled from Section 2 of the resubmission

6.10 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. The PSCR argued the evaluation was overly focused on the results of the 6MWT from the randomised controlled study and ignored functional/disability clinical evidence presented in study ENB-006-09/008-010. The ESC agreed that the evidence from ENB-006-09/008-010 did demonstrate that treatment with asofotase alfa rch resulted in improvements in some measures compared to baseline, however considered that the interpretation of these results was hampered by the lack of comparative data. The pre-PBAC response restated that patients enrolled in Study ENB-006-09/008-10 who had severe disability at baseline significantly improved after treatment with asfotase alfa. The response also maintained that the use of normative data to evaluate functional outcome, rather than a prospective controlled study, enables every patient to be their own control. This addressed any significant baseline heterogeneity across the study population for age, gender and/or height/stride length, while also catering for the impact of patient maturation over this extended observational period. The PBAC considered the significant baseline heterogeneity across the study population made a meaningful comparison difficult.

6.11 The ESC considered that it might be possible to identify a subset of patients with juvenile onset HPP with more severe disease, or from a limited age group, and who may derive the greatest benefit from treatment. This would potentially be a group that is continuous with the infantile onset population (eg. patients aged between 6 months and 3 or 5 years). A further analysis of the clinical trial data, including a comparison with results from the infantile onset population, would be informative in this regard. The pre-PBAC response contended the ESC proposal could potentially exclude a cohort of patients with significant disability who might receive a clinical benefit from asfotase alfa *rch.*

6.12 The economic model was based on the outcome of changes in the six-minute walk test (6MWT), as detailed in Table 4. Neither the randomised trial or open-label study presented used the 6MWT as a primary outcome; therefore, the economic model was reliant on a secondary outcome.

Comparative effectiveness

6.13 The results presented for whole trial/study populations remained unchanged from the previous submission. The results for 6MWT distance, which were transformed and then used in the economic model, are presented in Table 5.

Table 5: Key efficacy results

		ENB-009-10		ENB-006-09/ ENB-008-10
		AA	BSC[a]	AA
N		13/19	6	13
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)	[redacted]
		p=0.1303		
	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
	Week 144	[redacted]	[redacted]	[redacted]
	Week 192	[redacted]	[redacted]	[redacted]
	Week 240	[redacted]	[redacted]	[redacted]
Change from baseline in 6MWT distance, percent of predicted, mean metres (SD)	Baseline	73.33 (19.86)	76.93 (16.66)	59.06 (14.96)
	Week 24	[redacted]	[redacted]	19.38 (10.5)
		p=[redacted]		
	Week 48	[redacted]	[redacted]	22.20 (9.1)
	Week 96	[redacted]	[redacted]	20.80 (10.5)
	Week 144	[redacted]	[redacted]	30.60 (10.8)
	Week 192	[redacted]	[redacted]	25.28 (15.1)
	Week 240	[redacted]	[redacted]	23.24 (13.7)
Quality of life; change from baseline to Week 24; mean (SD)	LEFS	[redacted]	[redacted]	nr
		p=[redacted]		
	BPI-SF	[redacted]	[redacted]	nr
		p=[redacted]		
	CHAQ; mean disability score	nr	nr	-0.6364 (0.62); **p=0.0068**
	PODCI; parent assessed	nr	nr	[redacted]

[a] Placebo group crossed-over to AA at week 24

AA = asfotase alfa *rch;* BSC = best supportive care; N/A = not applicable; 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 Section 2 of the resubmission

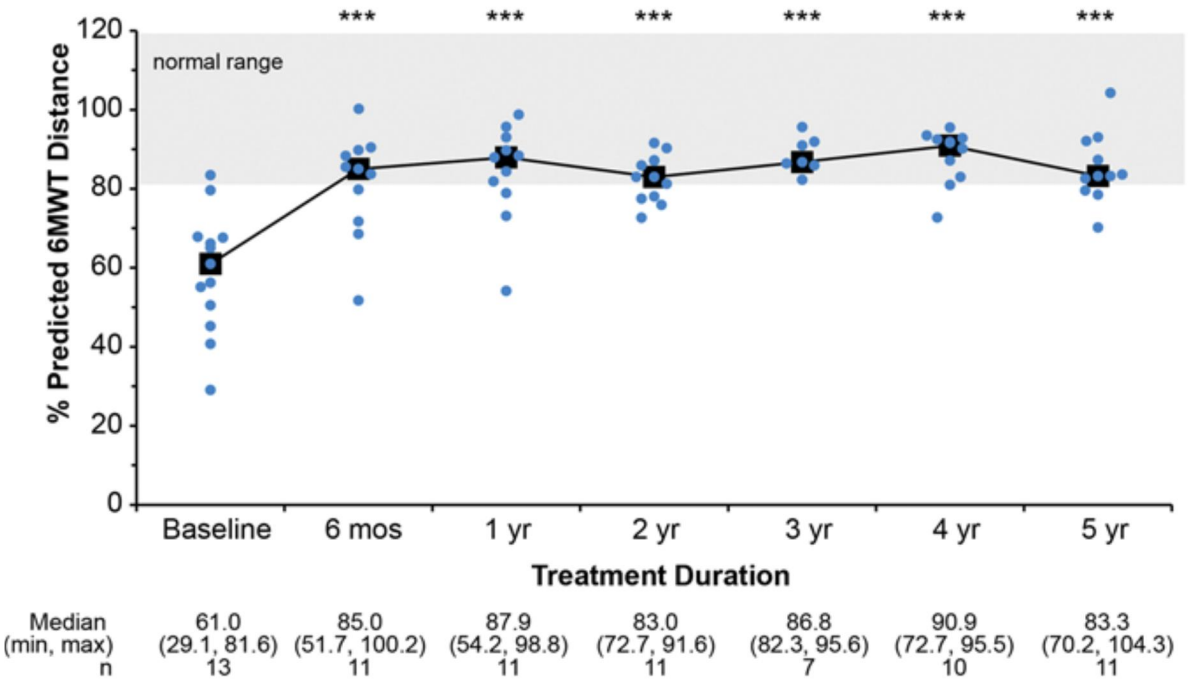
6.14 The resubmission estimated the minimal clinically important difference (MCID) for the change in 6MWT in children with HPP aged 5-12 years to be 30.2 metres (based on using the one-third standard deviation (SD) distribution-based approach, which was said to represent 8.8% of the mean baseline distance walked).

6.15 The economic evaluation relied on the results of the 6MWT, derived from the whole trial and study populations of ENB-009-10 and ENB-006-09/ENB-008-10. As for the previous submission, although the data presented showed that asfotase alfa *rch* improved 6MWT by more than the MCID estimated by the resubmission of 30.2 metres compared to BSC in Trial ENB-009-10, this difference was not statistically significant (p=0.1313). Overall, there was insufficient evidence to demonstrate that asfotase alfa *rch* improved 6MWT distance compared to control group patients from this trial. The pre-PBAC response claims the ESC have determined that the inability to demonstrate a statistically significant difference relative to an untreated patient cohort to be the principal factor in the calculation of therapeutic utility of asfotase alfa *rch* and that in so doing the ESC has disregarded the observation of the

sustained improvement in functional independence in studies ENB-009-10 and ENB-006-09/008. The pre-PBAC response further argued that it is not practical or ethical to perform a multiyear evaluation using prospective controlled study design in ultra-rare genetic diseases. The PBAC noted this argument but considered it remained unclear whether, based on this sparse data, a meaningful change would be achieved across the heterogeneous population.

6.16 The PSCR argued that the data from ENB-006-09/008-010 suggest near normalisation of ambulation, relative to healthy peers (see Figure 1). However, the ESC considered these data difficult to interpret in the absence of any comparative data on untreated patients over the same period. The ESC noted that the PSCR claims with respect to other outcomes (BOT-2, HHD and PODCI) were similarly difficult to interpret.

Figure 1: Improvement in ambulation over 5 years following AA treatment in patients with infantile- or juvenile-onset HPP aged between 5 and 12 years of age at enrolment in Study ENB-006-09/ENB-008-10, relative to normative sample of matched peers (age, gender, height/stride length)



*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001; mean difference for each time point compared with baseline by paired t test. Median, min, max, and n values are given below each figure. For all graphs, individual dots indicate individual patient scores at each time point. Grey area represents the normal range. **Source**: Whyte et al, 2016 *JCI Insight*. 2016;1(9):e85971. doi:10.1172/jci.insight.85971 (Figure 2.2, March 2018 PBAC submission, pg

6.17 The resubmission also presented results for the infantile- and juvenile-onset HPP subgroups for some outcomes from Study ENB-006-09/ENB-008-10. As demonstrated for the whole study population, there was a statistically significant difference between those treated with asfotase alfa *rch* and historical controls for the outcomes of RGI-C and RSS among juvenile-onset patients in Study ENB-006-09/ENB-008-10. The results of the analysis for the 6MWT for the juvenile-onset and

infantile-onset subgroups in Study ENB-006-09/ENB-008-10 are presented in Table 6. The appropriateness of conducting these analyses requires consideration given the small patient numbers and as the analyses for RSS and 6MWT represent post-hoc analyses of secondary outcomes. No subgroup analysis was provided for patients in the key randomised Trial ENB-009-10. The ESC agreed with the evaluator that the patient numbers in the trial were too small to derive any meaningful conclusions.

Table 6: Results for ambulation as assessed by the 6MWT – full analysis set

		ENB-006-09/ENB-008-10		
		Infantile-onset HPP	Juvenile-onset HPP	Whole study population
N at baseline		5	8	13
Change from baseline in 6MWT distance, mean metres (SD)	Baseline	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]
	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
	Week 144	[redacted]	[redacted]	[redacted]
	Week 192	[redacted]	[redacted]	[redacted]
	Week 240	[redacted]	[redacted]	[redacted]
Change from baseline in 6MWT distance, percent of predicted, mean metres (SD)	Baseline	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]
	Week 48	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]
	Week 144	[redacted]	[redacted]	[redacted]
	Week 192	[redacted]	[redacted]	[redacted]
	Week 240	[redacted]	[redacted]	[redacted]

nr = not reported; SD = standard deviation; 6MWT = six-minute walk test; HPP = Hypophosphatasia; AA = asfotase alfa *rch*
Source: Table 2.5.8, pp117-118 of the resubmission

6.18 In relation to the subgroup analysis for 6MWT distance for patients in Study ENB-006-09/ENB-008-10, no statistical analysis was presented. Overall, there was no basis for the resubmission's assumption that juvenile-onset HPP patients treated with asfotase alfa rch would have a significantly improved 6MWT distance compared to patients treated with BSC.

6.19 No additional clinical trial data on quality of life was presented. The data presented in the previous submission showed a non-significant 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 (BPI-SF) for patients treated with asfotase alfa rch compared to BSC in Trial ENB-009-10. There was an improvement in the Childhood Health Assessment Questionnaire (CHAQ) mean disability score and Paediatric Outcomes Data Collection Instrument (PODCI) score for patients treated with asfotase alfa rch compared to historical controls in Study ENB-006-09/ENB-008-10. While the results suggested that asfotase alfa *rch* may improve quality of life, the results do not support a claim that treatment with asfotase alfa *rch* improves quality of life compared to BSC.

Comparative harms

6.20 Comparative harms from Trial ENB-009-10 remained the same as those presented in the previous submission. There was a statistically significant difference between patients treated with asfotase alfa rch compared with BSC in relation to "general disorders and administration site conditions" (risk difference 60.3% [95% CI: 11%], 85%).

Benefits/harms

6.21 The benefits/harms for patients with juvenile-onset HPP could not be elucidated given the lack of subgroup analysis of the juvenile population in Trial ENB-009-10.

6.22 However, as noted in the previous submission, no statistically significant differences in the 6MWT were observed in Trial ENB-009-10 for the whole trial population between asfotase alfa rch and BSC over a mean duration of exposure of 24 weeks.

6.23 Similarly, 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, based on data for the whole trial population.

Clinical claim

6.24 The resubmission described asfotase alfa *rch* in juvenile-onset HPP as superior in terms of comparative effectiveness over BSC and that it is a safe and transformative therapy.

6.25 The claim differed from the previous submission in relation to safety, with the previous submission claiming non-inferior safety.

6.26 The claim of superiority in comparative effectiveness was not adequately supported by the clinical evidence for the following reasons:

- While there was a statistically significant improvement in Radiographic Global Impression of Change (RGI-C) in Study ENB-006-09/ENB-008-10, in the absence of a concurrent control group in the study, the comparison to matched historical controls for the whole study population was subject to potential bias and considerable uncertainty, and this was further compounded by the resubmission's subgroup analysis in patients with juvenile-onset HPP.
- The clinical evidence provided in the resubmission did not adequately support the assertion that asfotase alfa rch will improve 6MWT for patients with juvenile-onset HPP.

6.27 As with the previous submission, the ESC noted the submission presented little justification to correlate biochemical measurement improvements with clinically relevant outcomes or clinically meaningful improvement in the juvenile population.

6.28 The data presented indicated that asfotase alfa *rch* is likely to be a safe therapy, however, as for the previous submission long-term safety is of concern given the lack of long-term safety data. The ESC agreed that due to the minimal long-term safety data this claim was not supported.

6.29 The PBAC considered the resubmission's claim that asfotase alfa *rch* is a transformative therapy in the proposed patient population was not adequately supported by the data presented in the resubmission.

6.30 The PBAC considered that the claim of non-inferior comparative safety was not supported by the data.

Economic analysis

6.31 The resubmission presented a modelled cost-utility analysis. While the methodological approach to the model was similar to that presented in the previous submission, it differed with respect to the following aspects:

- No mortality assumed from HPP due to exclusion of patients with onset of symptoms from 0-6 months of age, no invasive ventilation state, no separate utility value for children less than 5 years of age.
- Base case starting age of 4.6 years instead of 5.8 years, and all patients assumed to start in health state severity level III.
- New scoring of EQ-5D-5L resulting in new, higher utility values for each health state: slightly reduced decrements in utility values from severity level I to severity level II and from severity level III to severity level IV (but marginally increased decrement from severity level II to severity level III).
- Vial price for asfotase alfa *rch* reduced from $[redacted] to $[redacted] per mg and a reduced expenditure cap per patient from $[redacted] to $[redacted].
- An annual revenue cap.

6.32 Like the previous submission, the health states in the model were defined based on percent predicted 6MWT. This may not be reasonable as the 6MWT was not the primary outcome of the trial or study and no statistically significant differences were observed between groups for this outcome in Trial ENB-009-10 at 24 weeks. Additionally, while results were available solely for the patients with juvenile-onset HPP from Study ENB-006-09/ENB-008-10, the resubmission included all patients in the study in the calculations, although the results for the juvenile population in Study ENB-006-009/ENB-008-10 appeared to be comparable to the whole study population (see Table 6). Of further consequence to the reliability of the estimates was that while Trial ENB-009-10 was not restricted to patients with juvenile-onset HPP, the resubmission also assumed that the results from the whole trial population would be representative of the results for the juvenile-onset HPP population. This added a further layer of uncertainty to the input data used in the model.

6.33 A summary of the model structure and rationale for the modelled cost-utility analysis is presented in Table 7.

Table 7: Summary of model structure and rationale

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td>Time horizon</td><td>101 years in the model base case versus up to 54 months for asfotase alfa rch in the trials, and up to 15 years for best supportive care in the natural history studies</td></tr>
<tr><td>Outcomes</td><td>QALYs</td></tr>
<tr><td>Methods used to generate results</td><td>Five-state Markov transition model</td></tr>
<tr><td>Health states</td><td>The model included four alive health states (Severity levels I, II, III and IV) and overall death. The alive health states were based on two times the estimated MCID of 8.8% calculated for percent-predicted distance on the 6MWT (see below).
<table>
<tr><th>Alive health states in the economic model</th><th>Definition</th></tr>
<tr><td>Severity level I</td><td>6MWT score >82.4% of predicted value</td></tr>
<tr><td>Severity level II</td><td>82.4%≥ 6MWT score >64.8% of predicted value</td></tr>
<tr><td>Severity level III</td><td>64.8%≥ 6MWT score >47.2% of predicted value</td></tr>
<tr><td>Severity level IV</td><td>6MWT score ≤47.2% of predicted value</td></tr>
</table>
6MWT = six-minute walk test
Source: Section 3.2, p246 of the resubmission

The definitions of the severity levels varied slightly compared to the previous submission, as the previous submission used an MCID of 8.9%.
While the resubmission provided more justification for the use of 6MWT as a surrogate outcome, it did not address the validity of the outcome using the surrogate to final outcomes working group framework. Overall, it was not apparent that use of the 6MWT would be adequate to define the severity health states, since the 6MWT does not capture additional features of HPP such as skeleton and joint deformity and renal and neurological complications.</td></tr>
<tr><td>Utilities</td><td>The utilities applied to the alive health states are summarised below.
<table>
<tr><th>Alive health states</th><th>Utility</th></tr>
<tr><td>Severity level I</td><td>0.93</td></tr>
<tr><td>Severity level II</td><td>0.78</td></tr>
<tr><td>Severity level III</td><td>0.61</td></tr>
<tr><td>Severity level IV</td><td>0.25</td></tr>
</table>
Source: Table 20, p263 of the resubmission

Despite the change in definition of the alive health states, the utility values were elicited as described in the previous submission based on EQ-5D-5L scoring of the same patient descriptions by nine clinicians from the UK/Canada/Germany. Apart from an updated scoring of the data based on a final mapping framework reported by Devlin et al 2016, rather than the interim mapping reported by van Hout et al 2012 that was used in the previous submission, the resubmission's approach to calculating utility values was the same as that described previously. In brief, the PBAC previously stated that the approach taken "lacked consistency and coherence" (Table 8, p16, Asfotase alfa rch PSD, July 2017).</td></tr>
<tr><td>Cycle length</td><td>12 weeks; a half-cycle correction was applied for the first and the last cycle</td></tr>
<tr><td>Transition probabilities</td><td>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=35 for BSC and n=343 for asfotase alfa rch) and were applied consistently in the model over a time horizon of 101 years.</td></tr>
</table>

Source: Constructed during the evaluation from Section 3 of the resubmission.

6.34 Key drivers of the economic evaluation are summarised in Table 8.

Table 8: 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. BSC transitions only based upon 35 data points, with 24 weeks of follow-up.	High, favours asfotase alfa *rch*
Alive health states	It was not apparent that health states defined by per cent predicted 6MWT adequately represented all alive patients with juvenile-onset HPP given other symptoms associated with the condition may not be captured by this measure. Reinforced by poor correlation between actual symptoms of patients in studies and the disease categories they were assigned to.	High, favours asfotase alfa *rch*
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 7, respectively. It was not apparent that there would be an improvement in utility values for patients treated with asfotase alfa *rch*, as there wasn't a significant difference in quality of life compared to BSC shown in the direct randomised trial ENB-009-10.	High, favours asfotase alfa *rch*
Costs	The resubmission assumed that asfotase alfa *rch* 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 high risk of injection site reactions, and the potential for anaphylactoid/anaphylactic reactions. The resubmission did not include a cost for management of injection site reactions. The resubmission used ex-manufacturer costs rather than dispensed prices for asfotase alfa *rch*, which underestimated the overall cost. The resubmission applied the same disease management costs to patients of all ages. While disease management costs may not be as high as the $90,963 estimated in the previous submission for patients under 5 years of age not on invasive ventilation (particularly given that patients with onset of symptoms prior to 6 months were excluded), disease state management costs in younger patients may be significantly higher than disease state management costs for older patients.	Low impact, uncertain which group is favoured

6MWT = six-minute walk test; BSC = best supportive care;
Source: Compiled during the evaluation

6.35 Results of the economic evaluation are presented in Table 9.

Table 9: Results of the economic evaluation, assuming age of initiation of treatment is at 4.6 years

Component	Asfotase alfa *rch*	Best supportive care	Increment
Costs	$ [redacted]	$250,397	$ [redacted]
Quality adjusted life years	17.57	6.23	[redacted]
Incremental cost/extra quality adjusted life year gained			**$** [redacted]

Costs incorporate the proposed annual asfotase alfa *rch* cap of $ [redacted] per patient per year
Source: Table 6 and 8, in Section 3 of the resubmission

6.36 Although the PBAC previously suggested that a resubmission should consider identifying a patient population where use of asfotase alfa *rch* would be more cost-effective, the resubmission did not do this.

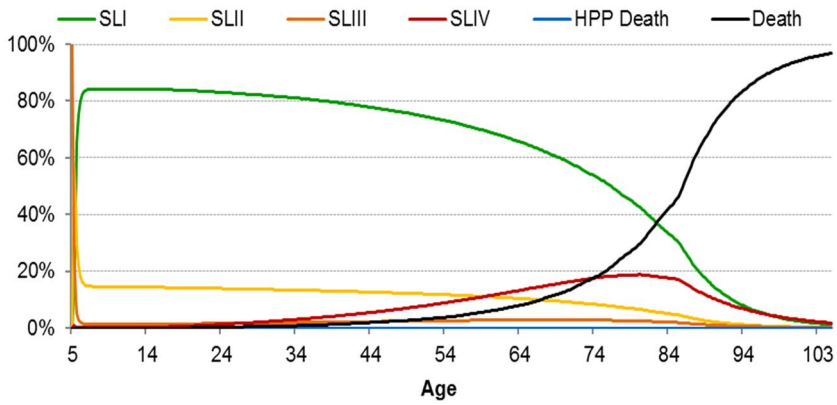
6.37 As for the previous submission, 6MWT may not be an acceptable surrogate outcome for patients with juvenile-onset HPP, particularly for those aged less than 5 years where 6MWT was not (and could not be) assessed in the trial or study. The resubmission did not address the validity of using a surrogate (6MWT) to final, patient relevant, outcome consistent with the PBAC Guidelines V5.0. The PSCR argued the 6MWT has been identified by UK-based expert clinicians as the measure available from asfotase alfa studies that most closely approximate the latent severity

of the disease. The ESC noted that the data comparing actual patient symptoms showed very poor alignment with the disease severity states derived from 6MWT (Table 10).

6.38 For the base case, patients initiated treatment aged 4.6 years and there was no difference in mortality assumed between the treatment arms. Based on the model presented, generally more asfotase alfa *rch* treated patients remained in the less severe HPP health states over the time horizon in the model (and subsequently a utility gain of 0.68 for much of the life span of most asfotase alfa *rch* patients versus untreated patients). 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 6 months and older.

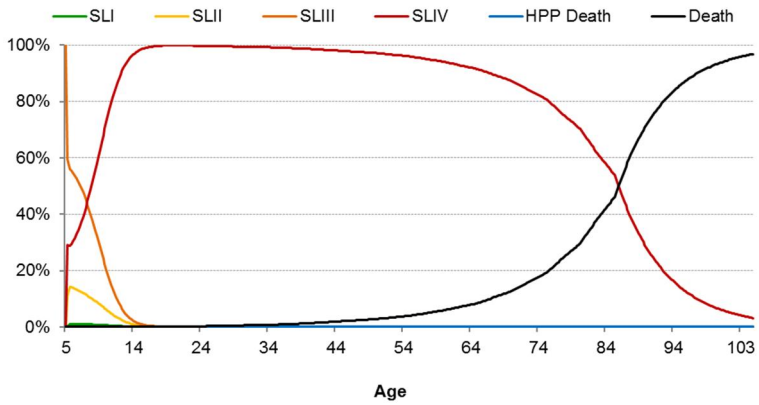
6.39 The Markov traces for the model, for the asfotase alfa *rch* and BSC groups are presented in Figures 2 and 3, respectively. Figure 4 shows the incremental QALYs accumulated over time in the model for the asfotase alfa *rch* and BSC groups, noting that the predicted QALYs do not plateau until a patient reaches approximately 95 years of age for those treated with asfotase alfa *rch*.

Figure 2: Markov trace for asfotase alfa *rch*: Base case



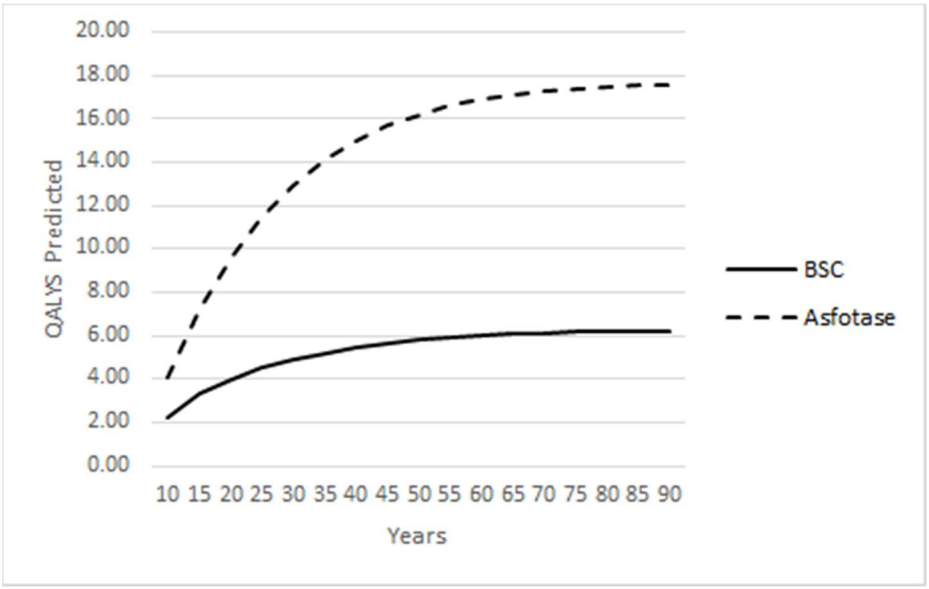
Source: Figure 5, in Section 3 of the resubmission

Figure 3: Markov trace for best supportive care: Base case



Source: Figure 6, in Section 3 of the resubmission

Figure 4: Incremental QALYs over time



Source: Determined during the evaluation

6.40 As for the previous submission, the base case ICER estimated in the resubmission was more than $1 million per QALY gained.

6.41 The ICER calculated by the resubmission for the base case, and for all sensitivity analyses, was highly dependent on the utility values for the health state severity levels. The ICERs calculated by the resubmission were considered to be highly uncertain for the following reasons:

- As for the previous submission, movement between the alive health states in the model was based on a comparison of asfotase alfa *rch* to historical control patients, with the comparative analyses considered to be biased in favour of asfotase alfa *rch*. Little confidence could be placed in the results, which were based on a small number of transitions over a short period of time, especially when the results were modelled out to a patient lifetime.
- 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 ICER was highly dependent on the utility value for severity level IV. With the lack of correlation between the case description used to derive the value and the HPP symptoms/complication rates for severity level IV (as shown in Table 12 of the PSD July 2017 for the previous submission and reproduced here as Table 10), little confidence could be put on the ICER estimated by the resubmission. The ESC noted that for some of the symptoms reported in Table 10, the proportion of patients experiencing such symptoms appear to suggest that severity level II is worse than severity level IV.
- The ESC advised that there was a high degree of uncertainty in the costs included in the model which were estimated from disease state descriptions, expert consultation, and sponsored studies in other countries.
- The resubmission continued to assume self-administration, whereas the high risk of injection site reactions, and risk of anaphylaxis/anaphylactoid reactions highlighted that administration under medical supervision could be required.
- The model assumed patients who fail to improve would continue treatment, contrary to treatment criteria.

Table 10: 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

6.42 To investigate some of the uncertainty surrounding the economic evaluation, the resubmission 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 4.6 years indicated that the model was most sensitive to a change in utility values and starting age of the patients, with the ICER increasing to more than $200,000 per QALY gained for utility values as calculated plus two standard errors, and to more than $1 million for an average age of treatment initiation of 42.2 years.

6.43 Given the similarity of symptoms and complications between severity levels III and IV (depicted in the Table 12 of the Executive Summary commentary on the previous submission), a sensitivity analysis was also undertaken during the evaluation, which assumed the same utility value for severity level IV as for severity level III and this increased the ICER to over $1 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 as for the previous submission, the health state specifications used and the utility values assigned to those health states were critical to the ICER.

6.44 In probabilistic sensitivity analyses presented in the resubmission, while variations in health state starting level, mean age at baseline, utility values, costs and 6MWT ordered-probit estimates resulted in variation in costs between approximately $10 - $20 million and $10 - $20 million over a patient lifetime, the resubmission indicated that there would be a small chance that the expected incremental QALYs could drop to as low as nil. The probabilistic sensitivity analyses illustrated the high level of uncertainty surrounding the likely cost-effectiveness of asfotase alfa *rch*, should it be listed on the PBS for patients with juvenile-onset HPP as requested.

Drug cost/patient/year

Table 11: 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/ patient/ week	Total mg dispensed/year	Cost[c]	
						Without cap	With cap
0.5-1[d]	*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]

NA =Not applicable (the resubmission stated this was not applicable to juvenile-onset HPP patient population)

[a] according to age ranges and mean weights reported on 'Cost of drug to PBS' and 'Background and assumptions' worksheet in Asfotase _alfa_Section4.xls, provided with the resubmission

[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] per mg (requested ex-manufacturer price): estimates assume 96% compliance

[d] not reported in the spreadsheet, but appears to be based on the details provided for those aged 0-1 years in the previous submission

Source: Compiled during the evaluation from the Section 4 MS Excel Workbook provided with the resubmission

6.45 It was not apparent why the resubmission calculated a cost for patients aged 0.5-1 year, without detailing the average weight, mg/dose or total mg dispensed per year for this age group. The resubmission stated that these details were not applicable to patients with juvenile-onset HPP. It appeared however, that the resubmission used the same average patient weight of 5.3 kg for this age group in the previous submission, an assumption of 10.6 mg/dose, dispensing of an 18 mg vial strength and 3 vials dispensed per week with a total of 2,808mg dispensed per year.

6.46 The drug cost per patient per year was lower than those derived in the previous submission, due to the price reduction and lower annual per patient cap.

Estimated PBS usage & financial implications

6.47 This resubmission was not considered by DUSC. The resubmission followed an epidemiological approach to estimate the number of patients with juvenile-onset HPP in Australia over the analysis period of 2018 to 2023. As there was limited

published data on prevalence, the resubmission estimated prevalence rates by age group. The estimated use and financial implications of listing asfotase alfa *rch* on the PBS is summarised in Table 12. The ESC noted from the evaluation that prevalence rates could be as high as 1:6000 for patients with milder forms of the disease. The PSCR maintained the majority of these patients were likely to have odontohypophosphatasia and would not qualify for PBS subsidy. Nonetheless, the ESC considered prevalence rates remained highly uncertain.

Table 12: Estimated use and financial implications

	Year 1 (2018)*	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Estimated extent of use						
Total number of patients treated						
- 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 *rch* (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/DHS**	-$	-$	-$	-$	-$	-$
Net cost to PBS/RPBS/MBS/DHS	$	$	$	$	$	$

*Part year: assumed PBS listing for 58.3% of 2018

**While the resubmission estimated that 2.25% of patients would be administered asfotase alfa *rch* under medical supervision, it did not include these costs in its estimation of the overall net cost to the PBS/RPBS.MBS.DHS. These costs were included during the evaluation, with revised figures shown in italics.

[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 resubmission calculated that two packs would be required per prescription

Source: Tables 4.7 and 4.9, pp295-296 of the resubmission and MS Excel Workbook: Section 4 model provided with the resubmission

6.48 The resubmission's approach to the financial implications remained the same as for the previous submission, with the exception that the submission proposed a reduced per patient cap of $ per annum, and annual revenue caps. The ESC advised that these proposals ameliorate the uncertainties identified in the July 2017 ESC advice to the PBAC for asfotase alfa *rch* as follows:

- Uncertainty in the eligible population because the prevalence population could be higher than that reported in the submission, noting the difficulties in determining the number of patients with this condition.
- Uncertainty in the number of eligible patients who would be diagnosed and treated in each age group, with use in older patients resulting in a higher cost due to weight-based dosing. This is addressed by the per patient cap for patients >=7 (the age at which this cap is most likely to take effect) and partly addressed by the annual expenditure cap, but only if overall usage exceeds

that cap.

- High uncertainty regarding the average body weight of Australian patients compared to patients in the trials. This is addressed by the per patient cap for patients >=7 (the age at which this cap is likely to take effect) and partly addressed by the annual expenditure cap, but only if overall usage exceeds that cap.
- Costs associated with administration under medical supervision and costs of treating injection site reactions. This is not addressed by either cap proposal.
- Use outside the proposed restriction of juvenile-onset HPP in adult patients where the proposed criteria for the restriction in proving juvenile-onset HPP may not be reliable. This is addressed if the annual expenditure caps are considered reasonable, noting the difficulties in determining the number of patients with this condition.

6.49 At Year 6, the resubmission estimated the number of patients would be less than 100 (in the previous submission) and the net cost to the PBS would be $20 - $30 million in Year 6 ($20- $30 million in the previous submission) of listing. The ESC noted the resubmission proposed a reduced per patient cap of $ per annum, and annual revenue caps (see Financial Management – Risk Share Arrangements, below). The ESC advised that these proposals would ameliorate some of the financial risks identified in the previous submission, as follows.

6.50 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 and there could be variation in the proportion of patients in each age group compared with what is reported. Additionally, 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 resubmission is subjective. This is addressed if the annual expenditure caps are considered reasonable.

6.51 Uncertainty in the costs since the resubmission assumed average body weight to be the same as average body weight in the trial and study. This is addressed by the per patient cap for patients >=7 (the age at which this cap is most likely to take effect) and partly addressed by the annual expenditure cap, but only if overall usage exceeds that cap.

6.52 However, the ESC commented that, whilst the financial caps proposed mitigated some of the financial risks, they did not correct the considerable concerns in the cost-effectiveness assessment of asfotase alfa *rch* in the proposed population.

6.53 Overall, the resubmission estimated that only about 20% of the eligible patient population with juvenile-onset HPP would be treated. Table 13 provides the resubmission's estimates of the eligible patient population.

Table 13: Estimation of the number of eligible patients with juvenile-onset HPP

Age group	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
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 4.6, p294 of the resubmission

The redacted table shows that at year 6, the total number of patients eligible for asfotase alfa was less than 1,000.

6.54 In a sensitivity analysis undertaken during the evaluation (Table 14), 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 6 of listing, an almost 3-fold increase on the resubmission's base case estimates. The ESC noted that the annual expenditure caps aim to address this risk.

Table 14: Sensitivity analysis on financial estimates

		Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Base case cost to PBS		$	$	$	$	$	$
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 juvenile-onset HPP	Decreased by 50%	$	$	$	$	$	$
Treatment rates for juvenile-onset HPP	Decreased by 50%	$	$	$	$	$	$
Diagnosis and treatment rate in patients 18 years and over	Same as diagnosis and treatment rate in patients aged 12-17 years	$	$	$	$	$	$

HPP = hypophosphatasia
Source: Table 4.14, p299 of the resubmission

6.55 The estimates were lower than those in the previous submission, with a base case estimate in Year 5 of listing of about $10 - $20 million compared to $20 - $30 million in the previous submission. The resubmission's revision of the likely diagnosis/uptake rates was considered to partly account for this reduction with the resubmission assuming substantially lower uptake rates, along with a reduction in use for patients aged 0 to 6 months at diagnosis.

Quality Use of Medicines

6.56 As in the previous submission, the resubmission stated that to ensure that asfotase alfa *rch* is administered correctly, in the right dose and regimen for the right patient, the resubmission proposed to develop a Patient Support Program. The resubmission indicated that the program would be implemented by specialist treating centres so that patients receive consistent information about their treatment as well as access to training on self-administration of injections and ongoing support in the home when establishing their treatment schedules.

6.57 The resubmission stated that the sponsor was willing to include terms in a Deed of Agreement in relation to a Patient Support Program and to discuss any other options considered by the PBAC or its subcommittees such as DUSC to ensure appropriate use.

Comparative harms Financial Management – Risk Sharing Arrangements

6.58 To ensure equity of access to all patients based on their disease severity rather than their body weight, the resubmission proposed a Risk Share Arrangement (RSA) with an annual per patient cap of $[redacted] per year, compared to $[redacted] in the previous submission. The financial estimates and the economic evaluation provided in the resubmission contained this cap.

6.59 The PSCR noted the commentary omitted references to the overall revenue cap presented in the submission. The ESC noted the proposed revenue caps (Table 15) and advised there was insufficient information presented to determine if these caps address all areas of uncertainty in the financial implications.

Table 15: Alexion proposed caps

Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source Alexion submission to March 18 PBAC, table 4.9

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 juvenile-onset hypophosphatasia (HPP) on the basis of continuing uncertainty about the magnitude of effect in the heterogeneous group of patients proposed in the submission. However, the PBAC considered it is likely that there is a group of patients who would derive the most benefit most from treatment with asfotase alfa *rch* but that it was not possible to identify that group on the basis of the information provided in the current submission. The PBAC considered that the submission presented a very high and uncertain ICER and that the proposed risk share agreement (RSA) was unlikely to mitigate the considerable concerns of financial risk.

7.2 The PBAC agreed with the ESC that 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 acknowledged the proposed restriction criteria would likely define a population with significant disability but further consultation with a rare diseases expert would be required to implement a workable restriction. There may be a case to argue for continued PBS access only once initiated in a specialist centre, rather than enforcing complicated PBS eligibility criteria. However, the cost-effectiveness of PBS access would still require further consideration.

7.3 The PBAC noted that asfotase alfa *rch* is currently being considered for inclusion in the Life Saving Drugs Program (LSDP) for the treatment of the most severe forms of HPP, perinatal- and infantile-onset disease.The PBAC recalled from the July 2017 meeting, that there was likely to be a survival advantage associated with treatment with asfotase alfa *rch* in patients with perinatal- and infantile-onset HPP who are at high risk of premature death. However, a survival benefit for asfotase alfa *rch* in patients with juvenile-onset (6 months to 17 years) HPP was not evaluated in the July 2017 submission as the clinical manifestations in this cohort are not associated with short-term mortality.

7.4 The PBAC recalled that in July 2017 it considered that a major resubmission for asfotase alfa *rch* in juvenile- and adult-onset HPP would need to establish both the clinical and cost effectiveness of treatment compared with best supportive care (BSC). With this in mind the PBAC noted that no new clinical evidence was provided and the data presented in resubmission excluded the three studies of asfotase alfa *rch* in patients with perinatal- and infantile-onset HPP. Therefore, the PBAC noted that the submission was based on one head-to-head randomised trial (ENB-009-10) comparing asfotase alfa *rch* (n=13) with best supportive care (n=6), two supplementary non-randomised studies (ENB-006-09 and ENB-008-10) and a retrospective epidemiological review of patients receiving BSC. As with the original submission the PBAC considered 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 of asfotase alfa *rch* in the juvenile-onset HPP population. The PBAC again noted the lack of statistically significant differences observed in the randomised trial for improvement in 6MWT, which forms the basis of the economic model, and quality of life. The PBAC considered the argument presented in the Pre-PBAC response in regards to the inability to demonstrate statistical significance, however, it was of the view that the lack of justification to correlate biochemical measurement improvements with clinically relevant outcomes and significant baseline heterogeneity across the study population made a meaningful comparison difficult; therefore an improvement in morbidity for patients with juvenile-onset HPP was not adequately supported by the submission.

7.5 The PBAC agreed with the ESC that the evidence from ENB-006-09/008-010 demonstrated that treatment with asfotase alfa *rch* resulted in improvements in

some functional/disability measures compared to baseline (e.g. 6MWT, BOT-2), however considered that the interpretation of these results was hampered by the lack of comparative data for untreated patients over the same period. The PBAC considered there may be a subset of patients with juvenile onset HPP with more severe disease, or from a limited age group, who derive the greatest benefit from treatment and a further analysis of the clinical trial data, including a comparison with results from the infantile onset population, would be informative in this regard.

7.6 The PBAC considered the base case ICER presented in the resubmission (which included the impact of the proposed annual per patient cap of $[redacted] per year) remained unacceptably high at over $1 million per QALY gained. In the base case, patients began treatment at 4.6 years and and there was no difference in mortality assumed between the treatment arms. The PBAC considered that the ICERs presented in the submission were highly uncertain due to the following issues with the economic model:

- The model structure lacked clinical validity. The four alive health states in the model (severity levels I-IV) were based on percent-predicted distance on the 6MWT, which does not adequately reflect 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 which is therefore an inadequate surrogate for disease state severity for patients with juvenile-onset HPP. This was particularly the case for those aged less than 5 years where 6MWT was not assessed in either the randomised clinical trial or the single arm study presented and cannot be reliably and reproducibly measured in this age group. Furthermore, the only evidence presented with a control group comparison showed no significant difference in 6MWT between those who were treated with asfotase alfa *rch* and those who receive best supportive care.
- Movements between health states for patients treated with best supportive care were extrapolated based on a very limited number of transitions observed over a short period of time. Thus, little confidence could be placed in the results, especially when they were modelled over a patient's lifetime.
- The utilities for each of the alive health states in the model (based on change in 6MWT distance), remained uncertain as they were derived from clinical experts based on information describing patients with a wide range of symptoms, and there was a lack of correlation between the case descriptions and the HPP symptoms/complication rates associated with those descriptions. Acceptance of the model requires acceptance of a utility gain of 0.68 for much of the life span of most asfotase alfa *rch* patients versus untreated patients.

7.7 The PBAC considered the cost to the PBS may be higher that estimated in the submission due to multiple uncertainties in the submission, including disease prevalence, diagnostic criteria, use outside the proposed restriction, drug

administration costs and use in older patients resulting in a higher cost due to weight-based dosing. The PBAC noted the annual revenue caps proposed in the submission, however, it was of the view that the expenditure caps only came into force if overall usage exceeds the proposed caps.

7.8 The PBAC agreed with the ESC that the use of per patient caps and an annual expenditure cap did not address the cost-effectiveness concerns regarding asfotase alfa and that even if a specific patient population was identified in which cost-effectiveness might be improved compared with the current submission proposal, 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.

7.9 The PBAC did not consider that asfotase alfa *rch* met the criteria for 'rule of rescue' in regard to whether "the proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition". In its consideration of the previous submission, "[t]he PBAC acknowledged that asfotase alfa [*rch*] 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 or quality of life 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 [paediatric]-onset HPP, was not adequately supported by the submission". As highlighted above, the resubmission did not demonstrate statistically significant differences in terms of observed/predicted 6MWT distance or quality of life for patients with juvenile-onset HPP treated with asfotase alfa *rch* compared with BSC, thus the impact of treatment with asfotase alfa *rch* in terms of an improvement in morbidity for juvenile-onset HPP, continued to be inadequately supported by the resubmission. The supportive long-term open-label studies did not provide a sufficient basis to reverse this decision.

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 disappointed that a therapy which will address a clear unmet medical need has

not been made available to juvenile-onset HPP patients with severe disability and the inequity this creates for these patients compared to patients with perinatal/infantile-onset HPP where the PBAC has made a recommendation to the LSDP in 2017. Alexion nevertheless remains committed to work in partnership with the PBAC to find a solution to provide access to subsidised asfotase alfa for these patients and will work with PBAC and DoH on the potential of a new reapplication for consideration for a recommendation to the LSDP for access to therapy for juvenile- onset HPP patients.