

## 5.15 SEBELIPASE ALFA, Solution concentrate for I.V. infusion 20 mg in 10 mL, Kanuma<sup>®</sup>, Alexion Pharmaceuticals Australasia Pty Ltd

### 1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required PBS listing for sebelipase alfa for the treatment of patients with infantile onset lysosomal acid lipase deficiency (LAL-D). This was the first submission for sebelipase alfa.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of sebelipase alfa (plus best supportive care (BSC)) versus BSC alone in patients with infantile onset LAL-D (Table 1). It is implied that patients treated with sebelipase alfa will also receive BSC from herein unless otherwise stated.

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

Component	Description
Population	Patients diagnosed with infantile onset LAL-D, also known as rapidly progressive LAL-D or Wolman disease.
Intervention	Sebelipase alfa administered at a starting dose of 1mg/kg as an IV infusion once-a-week, with the option of dose escalation to 3mg/kg and then to 5mg/kg based on response to clinical and biochemical criteria.
Comparator	BSC comprised of: <ol style="list-style-type: none"> <li>1. Nutritional support</li> <li>2. Steroid therapy</li> <li>3. Blood transfusions</li> <li>4. Lipid lowering therapies <sup>a</sup></li> </ol>
Outcomes	Survival, Safety/tolerability
Clinical claim	In patients with infantile onset LAL-D, sebelipase alfa is superior in terms of effectiveness as measured by overall survival and non-inferior in terms of safety when compared to BSC. Sebelipase alfa offers improvements in key biochemical markers, liver related damage and growth which improves their development and allows them to have meaningful gains in their QoL.

BSC = best supportive care; LAL-D = lysosomal acid lipase deficiency; QoL = quality of life

<sup>a</sup> Lipid lowering therapies was also listed as part of BSC within the submission

Source: Table 1.1.1, p22 of the submission.

## 2 Background

### **Registration status**

- 2.1 Sebelipase alfa was first approved by the TGA on 18 May 2017, with an increase to the maximum recommended dose approved for patients with infantile onset LAL-D granted on 13 October 2021.
- 2.2 The approved TGA indication for sebelipase alfa is; “KANUMA® is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D).”

## 3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

<b>Name, restriction, manner of administration, form</b>	<b>Maximum quantity (packs)</b>	<b>Maximum quantity (units)</b>	<b>No. Of repeats</b>	<b>Dispensed price for maximum quantity<sup>a</sup></b>	<b>Proprietary name and manufacturer</b>
Sebelipase alfa, 20 mg/10 mL injection, 10 mL vial	1	1	11	\$█	KANUMA®, Alexion Pharmaceuticals Australasia Pty Ltd

<sup>a</sup> Dispensed prices for maximum quantity are calculated from ex-manufacturer price per 20 mg vial of \$█ (published/list price).  
Source: Table 1.4.1, p53 of the submission.

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<b>Category / Program:</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type</b>	Authority Required – non-immediate assessment by Services
<b>Condition:</b>	<del>Infantile onset</del> lysosomal acid lipase deficiency (LAL-D) ( <i>Wolman disease</i> )
<b>PBS indication:</b>	<del>Infantile onset</del> lysosomal acid lipase deficiency (LAL-D) ( <i>Wolman disease</i> )
<b>Treatment Phase:</b>	Initial treatment
<b>Clinical criteria:</b>	<p><del>Patient must have a confirmed diagnosis of infant onset LAL-D;</del>  <i>The condition must have been diagnosed in infancy</i>  AND  <del>Patient has documented absent or deficient LAL activity;</del>  <i>The condition must have documented abnormalities in the lysosomal acid lipase (LAL) gene</i>  AND  <i>The condition must not be any of the following conditions of similar presentation: (i) late onset LAL-D (cholesteryl ester storage disease), (ii) Niemann-Pick disease, (iii) Chanarin Dorfman syndrome, (iv) galactosemia, (v) fructose intolerance, (vi) specific disorders of amino acid metabolism</i>  AND  <del>Patient has rapid disease progression demonstrated by manifestation of one or more of the below:</del>  <ul style="list-style-type: none"> <li><del>–severe vomiting and diarrhoea/steatorrhea</del></li> <li><del>–growth failure/failure to thrive</del></li> <li><del>–abdominal distension due to hepatomegaly and/or splenomegaly</del></li> <li><del>–disturbance of coagulation</del></li> <li><del>–severe anaemia</del></li> <li><del>–abnormal liver function tests</del></li> <li><del>–sibling diagnosed with rapidly progressive course of LAL-D</del></li> </ul> </p>
<b>Treatment criteria:</b>	Must be treated by a paediatrician with experience in the diagnosis and management of metabolic diseases.
<b>Prescribing Instructions:</b>	<p><del>At the time of the authority application, medical practitioners should request the appropriate number of vials, to provide for a single infusion to cover the dose based on the patient's weight and as per the Product Information.</del>  <i>If necessary, seek an increase in the maximum amount of drug based on each of:</i>  <i>(i) the patient's weight (in kg),</i>  <i>(ii) dosing as outlined in the Product Information,</i>  <i>(iii) the provision of one infusion per original prescription,</i>  <i>(iv) rounding to the nearest whole vial sufficient to provide this dose.</i></p>
<b>Treatment Phase:</b>	Continuing treatment
<b>Clinical criteria:</b>	<p><del>Patient must have previously received PBS-subsidised treatment with this drug for this condition;</del>  AND  <del>Patient continues to survive and has not experienced hypersensitivity reactions which cannot be managed with standard treatment or are life-threatening.</del></p>
<b>Treatment criteria:</b>	Must be treated by a specialist with experience in the diagnosis and management of metabolic disease.
<b>Prescribing Instructions:</b>	<p><del>At the time of the authority application, medical practitioners should request the appropriate number of vials, to provide for a single infusion to cover the dose based on the patient's weight and as per the Product Information.</del></p>
<b>Treatment Phase:</b>	Grandfathering
<b>Clinical criteria:</b>	<p><del>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition;</del>  AND  <del>Patient continues to survive and has not experienced hypersensitivity reactions which cannot be managed with standard treatment or are life-threatening.</del></p>

<b>Treatment criteria:</b>	<del>Must be treated by a specialist with experience in the diagnosis and management of metabolic disease.</del>
<b>Prescribing instructions:</b>	<del>At the time of the authority application, medical practitioners should request the appropriate number of vials, to provide for a single infusion to cover the dose based on the patient's weight and as per the Product Information.</del>

Source: Tables 1.4.2, 1.4.3 and 1.4.4, p55-57 of the submission.

- 3.2 While the proposed restriction stated that PBS listing is being sought for infantile onset LAL-D, the wording in the proposed restriction was broad enough to allow use of sebelipase alfa in patients with later onset LAL-D in children and adults, known as cholesteryl ester storage disease (CESD). The pre-sub-Committee response (PSCR) proposed the addition of the following clinical criteria (i) The condition must be diagnosed by leukocyte-based assay  $\pm$  genetic testing and (ii) The condition must have documented laboratory findings that demonstrate LAL enzyme with no detectable or residual activity; the degree of LAL-D is considered life threatening in the absence of drug treatment. The PSCR stated that LAL activity analysis with a leukocyte-based assay is a confirmatory and efficient diagnostic test and forms part of routine work-up and infantile onset LAL-D can be diagnosed with reasonable diagnostic precision with this test. The PSCR noted that suspected LAL-deficient patients may be tested by genetic analysis; however, genetic testing that is performed routinely in Australia (point mutation analysis) has some limitations and some functionally important mutations are undetected in routine genetic screening. The PBAC agreed with the ESC that it would be appropriate for the restriction criteria to specify residual LAL enzyme activity as  $<1\%$ , to ensure use in patients with infantile onset LAL-D, rather than the broader LAL-D population (see paragraph 4.4).
- 3.3 There is currently only [REDACTED] in Australia with infantile onset LAL-D. [REDACTED] sebelipase alfa therapy via a compassionate access program. The PBAC noted that based on the amended restriction above there would be no need for transitioning arrangements (i.e. a grandfather listing), as it would not exclude such patients from accessing PBS-subsidised treatment.

## 4 Population and disease

- 4.1 LAL-D is an autosomal recessive lipid metabolism disorder caused by mutations in the lipase A lysosomal acid (*LIPA*) gene. The *LIPA* gene encodes lysosomal acid lipase (LAL), the enzyme that hydrolyses cholesteryl esters and triglycerides within low-density lipoprotein (LDL) particles.
- 4.2 LAL-D can present very early in life in infants, known as infantile onset LAL-D (historically known as rapidly progressive LAL-D or Wolman disease), or later in life in children and adults, as CESD. The main distinction between the subtypes is defined through LAL activity level. Patients with infantile onset LAL-D present with less than 1% or absent LAL activity, while patients with CESD demonstrate 1-10% LAL activity. The extent of tissue deposition of cholesteryl esters and triglycerides is directly

proportional to the severity of the disease and is inversely proportional to the age of presentation.

- 4.3 Patients with infantile onset LAL-D tend to display rapid and severe disease progression and, if left untreated, most die within 12 months of life. Severe malabsorption, undernourishment and failure to thrive ultimately lead to starvation, cachexia, liver and multi-organ failure and ultimately death. The prognosis for patients with infantile onset LAL-D is poor. In the natural history study LAL-1-NH01, the median duration from LAL-D diagnosis to death was 1.02 months and the median age at death was 3.71 months. According to the investigators in LAL-1-NH-01, the medical literature suggests that growth failure is a predominant clinical feature of LAL-D presenting in infancy, and that there was a plausible link between growth failure and early mortality (p39, LAL-1-NH01 CSR).
- 4.4 There are no disease-modifying treatments that significantly extend survival for patients with infantile onset LAL-D currently available either in Australia or globally. Infantile-onset LAL-D is rare, with an estimated incidence of 1 in 704,000 live births in Australia between 1980 to 1996 (Meikle 1999). This corresponded to an estimate of one patient every 2.3 years in Australia. As noted in paragraph 3.3, there is currently one known surviving patient in Australia, who was born and diagnosed with infantile onset LAL-D in 2021 and is currently treated with sebelipase alfa under a compassionate access program. The ESC noted the total number of individuals with LAL-D (including CESD) is estimated to be 142 to 297<sup>1</sup> and sebelipase alfa is TGA indicated as ERT for all of these patients (not just infantile onset LAD-D).
- 4.5 Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) enzyme that acts as ERT in patients with infantile onset LAL-D. It binds to mannose-6-phosphate receptors on hepatocytes and to mannose receptors on macrophages via glycans expressed on the protein. Subsequently, sebelipase alfa is internalised and localised to the lysosome, where it hydrolyses accumulated cholesteryl esters and triglycerides in LAL-deficient cells thereby reducing the pathological effects in affected tissues.

## 5 Comparator

- 5.1 The submission nominated BSC alone, defined as nutritional support, blood transfusions, steroids and lipid-lowering treatments, as the main comparator to sebelipase alfa plus BSC. This was an appropriate comparator.
- 5.2 The submission claimed that while historically haematopoietic stem cell transplants (HSCT) and liver transplants have occasionally been used as treatment options in patients suffering from infantile onset LAL-D, they have provided minimal success and are not commonly performed in Australian infants based on Australian transplant registry data. As such they were excluded as part of BSC. This was reasonable. The ESC

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<sup>1</sup> <https://www.tga.gov.au/sites/default/files/auspar-sebelipase-alfa-180614.pdf>

acknowledged that HSCT and liver transplant are not available to Australian patients for the primary treatment of infantile LAL-D; however noted that HSCT may be considered for children who develop antidrug antibodies (ADA).

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from a health care professional via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with sebelipase alfa observed in a patient with infant onset LAL-D and an adolescent patient with CESD. The health care professional suggested that sebelipase alfa may enable patients to become medically stable and suitable for a bone marrow transplant. The comments indicated the need for central venous access and the development of ADA may limit the use of sebelipase as a long term maintenance treatment. The health care professional indicated it would be appropriate to limit access to confirmed (rather than suspected) cases of infant onset LAL-D as timely access to genetic or enzymatic diagnosis is available.

### ***Clinical trials***

- 6.3 The submission was based on two single arm, open-label studies that evaluated the efficacy and safety of sebelipase alfa in patients with infantile onset LAL-D (LAL-CL03; n=9 and LAL-CL08; n=10). The results of these studies were provided both individually and pooled.
- 6.4 The submission presented a matching-adjusted indirect comparison (MAIC) of LAL-CL03 and LAL-CL08 performed against a matched subgroup of patients from the natural history study, LAL-1-NH01 (n=35). Patients in LAL-1-NH01 were divided into 'treated' patients (who received HSCT and/or liver transplant, n = 10) and 'untreated' patients (for those who did not receive these therapies, n=25). Of the untreated patients, 21 had early growth failure and this subgroup was considered to be the relevant comparator group in the submission.
- 6.5 It was also noted that the definition of BSC for the comparator, which excluded HSCT and liver transplant, was not the same as BSC when used alongside sebelipase alfa, as three patients treated with sebelipase alfa in LAL-CL08 also received subsequent HSCT or bone marrow transplants (see paragraph 6.24). As such, this may have biased the results in favour of sebelipase alfa and it may not have been appropriate to have excluded patients treated with HSCT from the comparator arm in the MAIC. The PSCR provided a revised survival analysis which excluded the three patients who received HSCT or BMT in LAL-CL08. Among the 16 patients in LAL-CL03 and LAL-CL08 that did not receive a transplant, 12 (75%) patients were alive at 12 months of age and 11

(69%) patients were alive at 24 months of age, compared to 0% at both timepoints in the matched population in LAL-1-NH01. The PSCR stated the results demonstrated that the survival benefit of sebelipase alfa remains substantial and largely unchanged compared with the matched cohort in LAL-1-NH01.

6.6 Details of the studies presented in the submission are provided in Table 2.

**Table 2: Studies and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
LAL-CL03 NCT01371825 VITAL	<p>Clinical Study Report: An open-label, multicentre, dose escalation study to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of SBC-102 in children with growth failure due to lysosomal acid lipase deficiency. Data cut-off date was 3 January 2018. Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of Sebelipase Alfa in Children With Growth Failure Due to Lysosomal Acid Lipase Deficiency (ClinicalTrials.gov: NCT01371825).</p> <p>Jones et al. Survival in infants treated with sebelipase alfa for lysosomal acid lipase deficiency: an open-label, multicentre, dose escalation study.</p> <p>Vijay et al. Long-term survival with sebelipase alfa enzyme replacement therapy in infants with rapidly progressive lysosomal acid lipase deficiency: final results from 2 open-label studies.</p>	<p>2018</p> <p>Date not provided.</p> <p>Orphanet Journal of Rare Diseases 2017; 12:25. <a href="https://doi.org/10.1186/s13023-017-0587-3">https://doi.org/10.1186/s13023-017-0587-3</a>.</p> <p>Orphanet Journal of Rare Diseases 2021; 16:13. <a href="https://doi.org/10.1186/s13023-020-01577-4">https://doi.org/10.1186/s13023-020-01577-4</a></p>
LAL-CL08 NCT02193867	<p>Clinical Study Report: A Phase 2, open-label, multicentre study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of sebelipase alfa in infants with rapidly progressive lysosomal acid lipase deficiency. Data cut-off date was 30 October 2018. Clinical Study In Infants With Rapidly Progressive Lysosomal Acid Lipase Deficiency (ClinicalTrials.gov: NCT02193867).</p> <p>Vijay et al. Long-term survival with sebelipase alfa enzyme replacement therapy in infants with rapidly progressive lysosomal acid lipase deficiency: final results from 2 open-label studies.</p>	<p>2019</p> <p>Date not provided.</p> <p>Orphanet Journal of Rare Diseases 2021; 16:13. <a href="https://doi.org/10.1186/s13023-020-01577-4">https://doi.org/10.1186/s13023-020-01577-4</a></p>
LAL-1-NH01 NCT-1358370	<p>Clinical Study Report: A retrospective natural history study of patients with lysosomal acid lipase deficiency / Wolfan phenotype. Data cut-off date was 11 March 2013. A Retrospective Natural History Study of Patients With Lysosomal Acid Lipase Deficiency/Wolman Phenotype (ClinicalTrials.gov: NCT01358370)</p> <p>Jones et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants.</p>	<p>2013</p> <p>Date not provided.</p> <p><i>Genetics in medicine</i>. 2016 May;18(5):452-8. <a href="https://doi.org/10.1038/gim.2015.108">https://doi.org/10.1038/gim.2015.108</a></p>

Source: Table 2.2.1, p65 of the submission.

6.7 The key features of the included studies are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ max follow-up duration	Risk of bias	Patient population	Primary outcome <sup>a</sup>	Use in modelled evaluation
<b>Sebelipase studies</b>						
LAL-CL03	9	OL, SA, 60 months	High	Infants with LAL-D with GF and onset before 6 months of age	Survival to 12 months	Transition probabilities, resource use
LAL-CL08	10	OL, SA, 36 months	High	Infants with LAL-D	Safety and tolerability	Transition probabilities, resource use
<b>BSC studies</b>						
LAL-1-NH01	35 (untreated + GF, n=21)	retrospective, observational, natural history study	High	Infants with LAL-D	Not defined	Transition probabilities

BSC = best supportive care; GF = growth failure; OL=open label; SA = single arm

<sup>a</sup>The studies all investigated numerous other outcomes related to survival and growth, and additional outcomes measuring liver and haematological parameters, liver and spleen volume, haemoglobin and platelet normalisation, gamma-glutamyl transferase (GGT), bilirubin, albumin, ferritin and ALP, dyslipidaemia and Denver score.

Source: Compiled from Section 2 of the submission.

- 6.8 Key differences between patients enrolled in LAL-CL03 and LAL-CL08 included (i) the requirement for patients in LAL-CL03 to be diagnosed with growth failure and have symptom onset before six months of age and (ii) patients in LAL-CL08 were treated with higher doses of sebelipase alfa than in LAL-CL03. Nonetheless, the evaluation considered it was unlikely that these potential transitivity issues were significant enough or would preclude the results from the two studies being pooled.
- 6.9 The submission noted several key differences between LAL-CL03, LAL-CL08 and LAL-1-NH01 that may cause heterogeneity between the studies. At diagnosis, untreated patients with early growth failure in LAL-1-NH01:
- Presented with higher median AST levels at diagnosis (350.0 U/L) compared with LAL-CL03 (125.0 U/L) and LAL-CL08 (99.5 U/L) at screening;
  - Had lower median haemoglobin levels at diagnosis (79.5 g/L) compared with those in LAL-CL03 (93.0 g/L) and LAL-CL08 (90.0 g/L) at screening; and
  - Had lower median WFA percentiles at diagnosis (0.4) compared with those in LAL-CL03 (3.1) and in LAL-CL08 (1.1) at screening.
- 6.10 The submission noted that LAL-1-NH01 enrolled patients diagnosed as early as 1985 and that possible reasons for poorer clinical manifestations in these patients may be related to an evolution in understanding disease management leading up to the periods in which LAL-CL03 and LAL-CL08 were conducted. However an analysis of the median age of death among patients treated before 2005 and after 2005 in LAL-1-NH01 was conducted which found no improvement in survival, with median ages of death of 3.6 months and 2.7 months, respectively. In the NICE evaluation of sebelipase alfa, a UK expert on behalf of the sponsor noted that there have been no major improvements in care for patients with infantile onset LAL-D, and even with the best supportive, and/or aggressive care, the outcome of an untreated infant with LAL-D will

be death in infancy (p60, consultee and commentator comments on the evaluation consultation document from Alexion Pharma UK)<sup>2</sup>. Similarly, the TGA has noted that in the natural history Study LAL-1-NH01, median survival was noted to be longer for patients who received HSCT (and/or liver transplant) compared to those who did not; however, survival is still quite poor with median age at death of 8.6 months. (p24, Australian Public Assessment Report for Sebelipase alfa, TGA June 2018). No adjustments to address these potential transitivity issues were made by the submission.

- 6.11 It was also unclear if there had been any changes in the diagnosis of infantile onset LAL-D over the time period of identification of patients in LAL-1-NH01 (1985 to 2010). The number of patients diagnosed for each year was not reported, but it was noted that the majority of patients (21 out of 35) included in the analysis in LAL-1-NH01 were diagnosed before 1995. (section 4.26-4.27, p 16-17 Second evaluation consultation document – sebelipase alfa for treating lysosomal acid lipase deficiency, NICE, issue date April 2016).<sup>1</sup>
- 6.12 The sebelipase alfa studies were considered to have a high risk of bias, as they were open label, non-comparative and non-randomised studies. Similarly, the natural history study was also considered to have a high risk of bias due to the lack of matching comparison, lack of blinding and likely selection bias as patients for the retrospective study were selected based on available data.
- 6.13 The dosage regimens of sebelipase alfa used in the studies were not entirely in line with the PI which recommends a starting dose for infants <6 months of age presenting with rapidly progressive LAL-D of 1 mg/kg administered as an IV infusion once weekly and that dose escalation to 3 mg/kg and then to 5 mg/kg may be considered in the case of persistent suboptimal clinical response. Comparatively, in LAL-CL03 patients used a starting dose of sebelipase alfa of 0.35 mg/kg once a week before the dose was escalated to 1 mg/kg once a week and in LAL-CL08 the sebelipase alfa dose was able to be titrated up to 7.5 mg/kg once a week.

### **Comparative effectiveness**

- 6.14 A summary of survival results at different timepoints is presented in Table 4 for the included studies. Table 5 presents the median age of death for patients in the three included studies. An overlay of the Kaplan-Meier curves of the pooled LAL-CL03 and LAL-CL08 study compared to the matched 'untreated' cohort from the LAL-1-NH01 study is presented in Figure 1.

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<sup>2</sup><https://www.nice.org.uk/guidance/gid-lysosomalacidlipasedeficiencysebelipasealfaid737/documents/committee-papers-3>

**Table 4: Results of survival for the included studies**

Parameter	LAL-CL03 (n=9)	LAL-CL08 (n=10)	LAL-CL03 + LAL- CL08 pooled analysis (n=19)	LAL-1-NH01 untreated patients with GF only (n=21)	LAL-1- NH01 all patients (n=35)
<b>Survival through 12 months of age, n (%)</b>					
No <sup>a</sup>	3 (33)	1 (10)	4 (21)	21 (100)	31 (89)
Yes	6 (67)	9 (90)	15 (79)	0	4 (11)
NA <sup>b</sup>	0	0	0	0	0
% surviving, (95% CI) <sup>c</sup>	67 (29.93, 92.51)	90 (55.50, 99.75)	79 (54.43, 93.95)	0	11 (NR)
KM estimate of survival to 12 months of age, (%)	67	90	79	NA	NR
<b>Survival through 24 months of age, n (%)</b>					
No <sup>a</sup>	4 (44)	2 (20)	6 (32)	21 (100)	32 (91)
Yes	5 (56)	8 (80)	13 (68)	0	3 (9)
NA <sup>b</sup>	0	0	0	0	0
% surviving, (95% CI) <sup>c</sup>	56 (21.20, 86.30)	80 (44.39, 97.48)	68 (43.45, 87.42)	0	9 (NR)
KM estimate of survival to 24 months of age, (%)	56	80	68	0	NR
<b>Survival through 36 months of age, n (%)</b>					
No <sup>a</sup>	4 (44)	2 (20)	6 (32)	21 (100)	33 (94)
Yes	5 (56)	6 (60)	11 (58)	0	2 (6)
NA <sup>b</sup>	0	2 (20)	2 (11)	0	0
% surviving, (95% CI) <sup>c</sup>	56 (21.20, 86.30)	75 (34.91, 96.81)	65 (38.33, 85.79)	0	6 (NR)
KM estimate of survival to 36 months of age, (%)	56	80	68	NA	NR
<b>Survival through 48 months of age, n (%)</b>					
No <sup>a</sup>	4 (44)	0	4 (21)	21 (100)	35 (100)
Yes	5 (56)	0	5 (26)	0	0
NA <sup>b</sup>	0	10 (100)	10 (53)	0	0
% surviving, (95% CI) <sup>c</sup>	56 (21.20, 86.30)	NA	56 (21.20, 86.30) <sup>d</sup>	0	0
KM estimate of survival to 48 months of age, (%)	56	NA	68	NA	NA
<b>Survival through 60 months of age, n (%)</b>					
No <sup>a</sup>	4 (44)	0	4 (21)	21 (100)	35 (100)
Yes	3 (33)	0	3 (16)	0	0
NA <sup>b</sup>	2 (22)	10 (100)	12 (63)	0	0
% surviving, (95% CI) <sup>c</sup>	43 (9.90, 81.59)	NA <sup>d</sup>	43 (9.90, 81.59) <sup>d</sup>	0	0
KM estimate of survival to 60 months of age, (%)	56	NA	68	NA	NA

CI = confidence interval; GF = growth failure; NA = not applicable

<sup>a</sup> Includes patients, if any, who were permanently lost to follow-up prior to the age specified in the analysis.

<sup>b</sup> Patients alive and discontinued study prior to reaching the age specified in the analysis. These patients were excluded from the Percent Surviving analyses and censored in Kaplan-Meier analyses.

<sup>c</sup> Exact confidence interval calculated using Clopper-Pearson method. Patients with unknown survival status at the age specified in the analysis were excluded.

<sup>d</sup> Survival up to 48 months and 60 months was only performed on results from LAL-CL03 as LAL-CL08 completed after 3 years.

Source: Table 2.6.1, p142 of the submission.

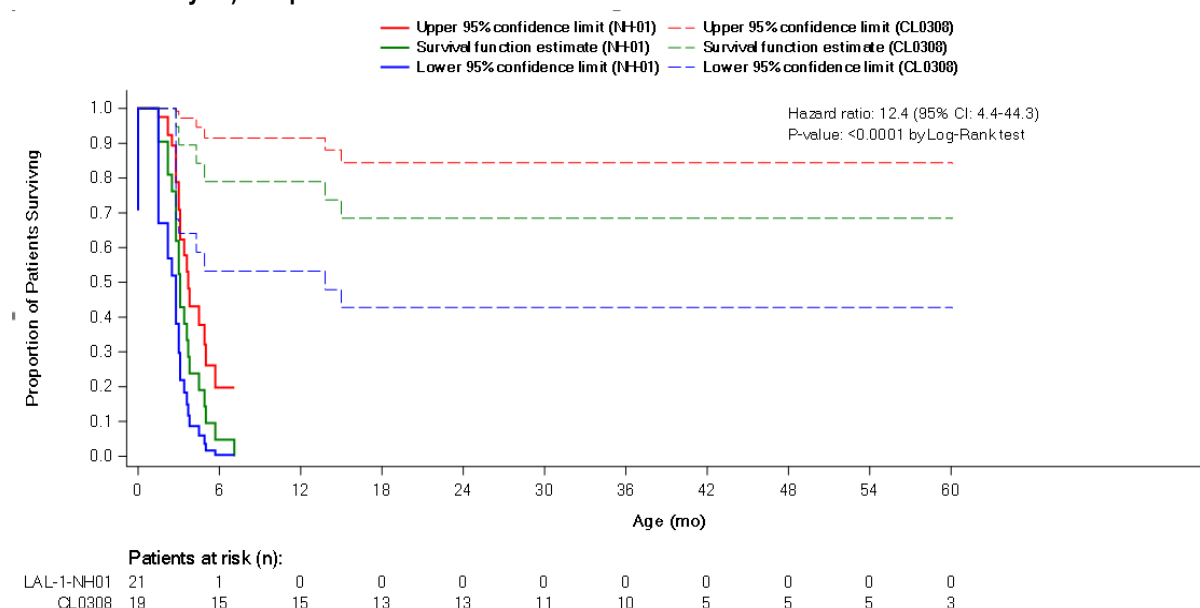
**Table 5: Median age of death for the included studies**

Trial ID	Number of patients who died during study, n/N (%)	Median age of death	Range
LAL-CL03	4/9 (44%)	3.6 months	2.8 – 15.0 months
LAL-CL08	2/10 (20%)	9.33 months	4.9 – 13.8 months
LAL-1-NH01 (untreated patients with GF)	21/21 (100%)	3.02 months	1.44 – 7.09 months
LAL-1-NH01 (all patients)	35/35 (100%)	3.71 months	1.44 – 46.32 months

GF = growth failure

Source: Table 2.5.21, p129 of the submission and data from Section 2.5 of the submission.

**Figure 1: Kaplan-Meier estimate of survival from birth to 60 months of age in LAL-CL03 + LAL-CL08 (pooled analysis) compared with matched 'untreated' cohort in LAL-1-NH01**



mo = month

Source: Figure 2.6.6, p155 of the submission

Note that the HR calculation was conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.15 In total, 15 (79%) of the 19 patients treated with sebelipase alfa in the pooled studies survived beyond 12 months of age, with 13 (68%) patients surviving to 24 months. The submission stated that there were no further deaths beyond 24 months across both studies and thus sebelipase alfa was assumed to reverse the course of infantile onset LAL-D when continuing treatment, with this assumption used in the economic model in the submission. It should be noted that patients from LAL-CL08 were only followed for 36 months and this time frame may not be adequate to support the conclusion that continuing treatment with sebelipase alfa reverses the course of infantile onset LAL-D with no further deaths from LAL-D in all sebelipase alfa treated patients.

- 6.16 The MAIC analysis population included the 19 patients across LAL-CL03 and LAL-CL08 and the 21 matched patients from LAL-1-NH01. i.e. the only matching was from the selection of patients who were ‘untreated’ and who presented with early growth failure. The hazard ratio for survival was estimated as 12.4 (95% CI: [4.4, 44.3],  $p < 0.001$ )<sup>3</sup> using the Cox Proportional Hazards Regression model with treatment as covariate, where the hazard ratio  $>1$  and favoured sebelipase alfa. The 95% CI was based on the Profile Likelihood estimate. These data appeared to support improved survival of patients with infantile onset LAL-D treated with sebelipase alfa (plus BSC) compared to BSC alone. However, given the small sample sizes of the included study, the actual hazard ratio was uncertain. Moreover, it was unclear if the benefit would be sustained for a lifetime time horizon as assumed in the economic evaluation.
- 6.17 The submission also provided information from a global registry for patients with LAL-D across all ages, regardless of treatment with sebelipase alfa, to support the submission. It was noted that since 2013, 22 patients with infantile onset LAL-D were enrolled in the registry, all of whom received treatment with sebelipase alfa, and one (4.5%) patient died on treatment due to hepatic failure. The median follow-up time was 2.1 years (range: 0.5-4.3 years). The Kaplan-Meier curves generated from registry data show a 94.4% survival rate up to 10 years of age, however given the limited follow-up time and small number of patients at risk (only three patients at risk at eight years of age, and one patient at risk at nine and ten years of age), the survival estimate should be interpreted with caution. The submission further claimed that the most commonly reported dose regimen used at any time among infants in the registry was 3 mg/kg once a week, with 20/22 patients ever receiving this dose regimen. No information about the highest dose received by patients on the registry was provided. It was noted that 11/21 (52.4%) of patients were listed as using ‘other’ sebelipase alfa dose and frequency at last known follow up (which could include dosages of  $>3$  mg/kg), suggesting that 3 mg/kg was not the most common dose used at last known follow up in the registry.
- 6.18 Measures relating to growth of the patient were reported as secondary outcomes in the studies with WFA and length/height for age data presented in Table 6. Increases in median WFA percentile and median length/height for age percentile was observed for patients in LAL-CL03 and LAL-CL08, whereas patients in LAL-1-NH01 observed decreases for these measures.

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<sup>3</sup> Note that the HR calculation was conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

**Table 6: Weight for age and length/height for age results for the included studies**

Trial ID	Baseline (range)	Week 144 (range)	Week 240 (range)
<b>Median weight for age percentile</b>			
LAL-CL03	3.076 (0.00 – 77.04); n=8	25.109 (14.04 – 91.38); n=5	25.189 (7.99-96.90); n=5
LAL-CL08	1.059 (0.00-79.95); n=10	67.536 (36.45, 87.55); n=5	NR
LAL-1-NH01 (untreated patients with GF)	0.4 (0 – 97); n=20 <sup>a</sup>	0.2 (0 – 79), n=20 <sup>b</sup>	NR
LAL-1-NH01 (all patients)	0.4 (0 – 97); n=30 <sup>a</sup>	0.3 (0 – 79), n=34 <sup>b</sup>	NR
<b>Median length or height for age percentile</b>			
LAL-CL03	1.789 (0.00 – 80.78), n=8	31.934 (12.67, 81.37); n=5	34.967 (2.84 – 96.09); n=5
LAL-CL08	2.872 (0.07, 68.08); n=9	56.092 (7.56, 60.59); n=5	NR
LAL-1-NH01 (untreated patients with GF)	3.1 (0, 58), n=5 <sup>a</sup>	1.6 (0 – 3); n=2 <sup>b</sup>	NR
LAL-1-NH01 (all patients)	2.6 (0 – 58), n=10 <sup>a</sup>	0.6 (0 – 12), n=9 <sup>b</sup>	NR

GF = growth failure; NR = not reported; WFA = weight for age

<sup>a</sup> Measurements taken prior to diagnosis

<sup>b</sup> Measurements taken prior to death

Source: Data from Section 2.5 of the submission, Table 13, p100 of the LAL-CL03 CSR, Tables 11 and 12, p71, 74 of the LAL-CL08 CSR, Tables 6.2, 6.2.1, 7.2 and 7.2.1 of the LAL-1-NH01 CSR

6.19 Median change in arm circumference-for-age, head circumference-for-age, body mass index-for-age and weight-for-length or height are presented in Table 7.

**Table 7: Median change from baseline (percentile) for ACFA, HCFA, BMIFA and WFL for eligible patients**

	<b>ACFA Median percentile (range)</b>	<b>HCFA Median percentile (range)</b>	<b>BMIFA Median percentile (range)</b>	<b>WFL Median percentile (range)</b>
<b>LAL-CL03</b>				
Baseline	0.011 (0.00, 0.62) (n=4)	22.46 (0.06, 86.43) (n= 8)	15.48 (0.0, 62.93) (n=8)	32.63 (0.10, 91.47) (n=8)
Change at last assessment	28.658 (18.12, 74.55) (n=4)	38.99 (13.5, 71.4) (n=6)	32.036 (-0.650, 87.79) (n=7)	25.55 (-34.99, 86.33) (n=7)
<b>LAL-CL08</b>				
Baseline	0.001 (0.00, 4.18) (n=5)	1.743 (0.00, 40.90) (n=9)	0.415 (0.00, 94.29) (n=9)	0.964 (0.01, 99.31) (n=9)
Change at last assessment	2.855 (0.31, 5.90) (n=4)	26.679 (-18, 61.28) (n=8)	54.144 (-9.44, 92.72) (n=9)	44.089 (-13.23, 90.05) (n=9)
<b>LAL-1-NH01 untreated patients with growth failure</b>				
First chart record	NR	36.7 (9, 90) (n=10)	43.6 (25, 83) (n=7)	47.2 (10, 90) (n=7)
Change at diagnosis	NR	-17.5 (-44, 0) (n=4)	-24.4 (-43, 0) (n=3)	12.0 (-42, 7) (n=3)
Change at death	NR	-36.7 (-44.4, -9.0) (n=2)	NR (n=0)	NR (n=0)
<b>LAL-1-NH01 all patients</b>				
First chart record	NR	29.8 (1, 90) (n=15)	28.7 (0, 83) (n=14)	35.5 (0, 90) (n=14)
Change at diagnosis	NR	-11.6 (-44, 0) (n=6)	-13.8 (-43, 0) (n=5)	12.0 (-42, 7) (n=5)
Change at death	NR	-13.0 (-44, -9) (n=4)	-0.1 (-14, 8) (n=3)	1.3 (-20, 10) (n=3)

ACFA = arm circumference-for-age; BMIFA = body mass index-for-age; HCFA = head circumference-for-age; NR = not reported; WFL = weight-for-length

Source: Tables 2.5.2, 2.5.12 and 2.5.22, p100, 115 and 132 of the submission, and Tables 8.2, 8.2.1, 9.2, 9.2.1, 10.2, 10.2.1 of the LAL-1-NH01 clinical study report

- 6.20 Improved nutritional status, measured by the number of patients underweight, wasting and stunting, was observed over time for patients in LAL-CL03 and LAL-CL08. None of the surviving patients met the criteria for stunting, wasting or underweight by Week 144 (LAL-CL03, 5 patients) or Week 48 (LAL-CL08, 8 patients), with this maintained by the majority of patients who continued to be followed through to end of study.
- 6.21 The results from all eligible patients in LAL-1-NH01 demonstrated deterioration in nutritional status amongst patients from birth to death. At birth, 20% (7/35) of the eligible patients were characterised as underweight and this increased to 66% (23/35) prior to death. Across all patient subgroups, there was an overall increase in patients that demonstrated signs of undernutrition as the study progressed.
- 6.22 Other endpoints were reported, including outcomes for liver and haematological parameters, liver and spleen volume, haemoglobin and platelet normalisation, gamma-glutamyl transferase (GGT), bilirubin, albumin, ferritin and ALP, dyslipidaemia

and Denver score. As the studies had small sample sizes and the results generally reported wide ranges, any interpretation should be done cautiously, but the pooled analysis of LAL-CL03 and LAL-CL08 suggest that symptoms such as spleen and liver volume, liver function, haemoglobin and platelet counts, and other relevant biochemical measures in patients treated with sebelipase alfa will improve and normalise over time compared to baseline.

- 6.23 The submission reported that a total of ten patients in either LAL-CL03 and LAL-CL08 developed anti-drug antibodies (ADAs), with the development of high-titre ADAs found to correlate with a reduced clinical response to sebelipase alfa.
- 6.24 In LAL-CL08, three patients had notably higher ADA titres than other patients in the study and for all three patients, the disease-causing mutation was a deletion of the entire *LIPA* gene. The absence of any *LIPA* gene product was hypothesised to be the root cause for the development of high titres of neutralising ADAs in these patients. In all three patients the development of high ADA titres was associated with diminished clinical efficacy observed though decreased WFA and other parameters of failure to thrive. This loss of efficacy prompted sebelipase alfa dose increases to 5 mg/kg or 7.5 mg/kg once weekly and other clinical measures, including immunomodulatory therapy (e.g. rituximab or bortezomib) and HSCT or bone marrow transplants. Improvement and/or stabilisation of clinical response was observed in two patients when ADA titres decreased after the introduction of immunomodulation therapy or after successfully engrafted HSCT or bone marrow transplant, and in the third patient, the condition appeared to have stabilised at week 140 based on WFA after dose escalation to 5 mg/kg, however as this was near the end of the study period it was unknown if the patient subsequently required any more management due to the high ADA titres. Unrelated to ADA titres, another patient in LAL-CL08 had a bone marrow transplant due to an inflammatory hemophagocytic lymphohistiocytosis (HLH)-type condition that failed to improve to a rapid dose escalation of sebelipase alfa.
- 6.25 The development of high ADAs titres indicated a plausible biological pathway for the waning of sebelipase alfa efficacy over time. It is unknown if this will also occur beyond the 156 week follow up period of LAL-CL08. Given that Australian patients will be restricted to a maximum dose of sebelipase alfa of 5 mg/kg (whereas patients could use a higher dose in LAL-CL08) and as the submission reported, that HSCT and bone marrow transplant for LAL-D were not commonly carried out in Australia, it was possible that management of high ADA titres could be different in Australia compared to LAL-CL08 which could lead to different (possibly worse) clinical outcomes. However it was acknowledged that there was likely little experience in management of high ADA titres in the Australian setting given only | currently being treated with sebelipase alfa in Australia.
- 6.26 The PSCR stated there is emerging evidence that a small proportion of patients with whole gene deletions who are past infancy and whose disease had been stabilised

with sebelipase alfa therapy could develop high titres of neutralising ADAs. This whole gene deletion affecting both alleles of the LIPA gene and cholesterol 25-hydroxylase gene can render a suboptimal clinical response to sebelipase alfa (Vijay et al. 2021). In these patients, HSCT, as an add-on therapy, is shown to be a potentially beneficial treatment that prevents waning and helps maintain the efficacy of sebelipase alfa (Potter et al. 2021).

### Comparative harms

6.27 Treatment-emergent adverse events (TEAEs) were reported for all 19 patients across both LAL-CL03 and LAL-CL08. The most frequently reported TEAEs (>50%) were diarrhoea, vomiting and pyrexia, all of which were reported for 15 (79%) patients. These were followed by gastroenteritis and cough, which were both experienced by 11 (58%) patients.

6.28 Table 8 and Table 9 provide details of the TEAEs reported in LAL-CL03, LAL-CL08 and a pooled analysis of the two studies.

**Table 8: Summary of treatment-emergent adverse events in LAL-CL03 and LAL-CL08**

System Organ Class	LAL-CL03 (n=9), n (%)	LAL-CL08 (n=10), n (%)	Pooled analysis (n=19), n (%)
Patients with at least 1 TEAE	9 (100)	10 (100)	19 (100)
Gastrointestinal disorders	8 (89)	10 (100)	18 (95)
Investigations	8 (89)	10 (100)	18 (95)
General disorders and administration site conditions	6 (67)	10 (100)	16 (84)
Infections and infestations	6 (67)	10 (100)	16 (84)
Respiratory, thoracic and mediastinal disorders	7 (78)	9 (90)	16 (84)
Skin and subcutaneous disorders	7 (78)	9 (90)	16 (84)
Blood and lymphatic system disorders	6 (67)	9 (90)	15 (79)
Metabolism and nutrition disorders	6 (67)	9 (90)	15 (79)
Injury, poisoning and procedural complications	5 (56)	9 (90)	14 (74)
Cardiac disorders	5 (56)	8 (80)	13 (68)
Vascular disorders	4 (44)	8 (80)	12 (63)
Product issues	2 (22)	9 (90)	11 (58)
Eye disorders	2 (22)	6 (60)	8 (42)
Psychiatric disorders	2 (22)	6 (60)	8 (42)
Renal and urinary disorders	1 (11)	5 (50)	6 (32)
Congenital, familial and genetic disorders	2 (22)	3 (30)	5 (26)
Hepatobiliary disorders	2 (22)	3 (30)	5 (26)
Immune system disorders	0	3 (30)	3 (16)
Ear and labyrinth disorders	2 (22)	0	2 (11)

TEAE = treatment emergent adverse events  
Source: Table 2.6.7, p151 of the submission

**Table 9: Overview of treatment-emergent adverse events in LAL-CL03 and LAL-CL08**

	LAL-CL03 (n=9) n (%)	LAL-CL08 (n=10) n (%)	Pooled Safety (n=19) n (%)
<b>Any TEAE</b>	9 (100)	10 (100)	19 (100)
Onset during infusion and ≤ 4 hours after end of infusion	6 (67)	9 (90)	15 (79)
Onset during infusion and ≤ 24 hours after end of infusion	8 (89)	10 (100)	18 (95)
Onset > 4 and ≤ 24 hours after end of infusion	8 (89)	10 (100)	18 (95)
<b>Any related TEAE<sup>a</sup></b>	6 (67)	8 (80)	14 (74)
Onset during infusion and ≤ 4 hours after end of infusion	5 (56)	7 (70)	12 (63)
Onset during infusion and ≤ 24 hours after end of infusion	5 (56)	8 (80)	13 (68)
Onset > 4 and ≤ 24 hours after end of infusion	3 (33)	6 (60)	9 (47)
<b>Any TESAE</b>	9 (100)	10 (100)	19 (100)
Any treatment-related TESAE <sup>a</sup>	1 (11)	5 (50)	6 (32)
Any infusion-associated reaction <sup>b</sup>	5 (56)	8 (80)	13 (68)
Any hypersensitivity and anaphylactic reaction <sup>c</sup>	8 (89)	9 (90)	17 (89)
Any TEAE leading to death	4 (44)	2 (20)	6 (32)
Any TEAE leading to study discontinuation	0	0	0
Any TEAE leading to study drug discontinuation <sup>d</sup>	2 (22)	0	2 (11)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in specified subgroup; n = number of patients with at least 1 TEAE in the category; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Note: The TEAEs were coded using MedDRA version 21.0. Percentage (%) was based on N.

<sup>a</sup> Based on Investigator's assessment of whether an event was at least possibly related to study drug.

<sup>b</sup> Based on Investigator's assessment of whether an event was an infusion-associated reaction.

<sup>c</sup> Includes hypersensitivity (narrow terms) and anaphylactic reactions (broad and narrow terms) by Standardised MedDRA Query.

<sup>d</sup> Due to two patients who died after the last infusion of sebelipase alfa.

Source: Table 2.6.8, p152 of the submission

- 6.29 Across both studies, all 19 (100%) patients experienced at least 1 serious adverse event (SAE), most commonly pyrexia which was reported for 9 (47%) patients. This was followed by gastroenteritis and vomiting, both of which were reported for 8 (42%) patients. Additionally, infusion-associated reactions were frequent due to the method of administration of sebelipase alfa.
- 6.30 Both LAL-CL03 and LAL-CL08 considered the impact of ADAs on safety. In LAL-CL03, incidence of infusion-associated reactions appears to have increased after ADA positivity in four patients, and of the five patients who reported any infusion-associated reactions, four were ADA positive. However, as severe AEs occurred in all nine patients in LAL-CL03, the relationship between ADA and SAE was less clear. In LAL-CL08, the CSR stated that a comparison of the frequency of infusion-associated reactions, SAEs, and TEAEs in all ADA-positive patients (after their initial positive result for ADAs) with patients who tested negative for ADAs throughout the study supported the lack of a clear impact of ADAs on safety. Overall, the relationship between ADA and safety was unclear but it was plausible that ADA development was correlated with increased adverse events.

## **Benefits/harms**

- 6.31 The data presented in the submission did not allow for a quantitative comparison of

the benefits and harms of sebelipase alfa and best supportive care. Accordingly, a benefits/harms table is not presented.

### **Clinical claim**

- 6.32 The submission described sebelipase alfa as superior in terms of effectiveness compared with BSC and non-inferior in terms of safety compared to BSC.
- 6.33 The claim of superior effectiveness was reasonably supported by the evidence presented in the submission, and it was likely that patients with infantile onset LAL-D treated with sebelipase alfa would derive a survival benefit compared to BSC alone. However, the magnitude and durability of the survival benefit was uncertain, because while the MAIC suggested superior survival for patients treated with sebelipase alfa compared to BSC (overall survival hazard ratio = 12.5, 95% CI 4.4, 44.3<sup>4</sup>), this comparison was based on studies with small sample sizes, with limited follow up duration for sebelipase alfa treatment (maximum of three and five years for LAL-CL08 and LAL-CL03, respectively, against a proposed lifetime treatment duration). Additionally, the potential for the development of ADA, as observed in LAL-CL03 and LAL-CL08, provided a plausible biological pathway for the efficacy of sebelipase alfa to wane over time. The ESC acknowledged the difficulty of obtaining data due to the rarity and high mortality of untreated infantile onset LAL-D.
- 6.34 Due to the absence of comparative safety data for sebelipase alfa or any safety data for LAL-1-NH01, it was not possible for the submission to present any type of direct or indirect safety comparison. It was therefore difficult to draw any conclusion regarding the relative safety of sebelipase alfa versus BSC.
- 6.35 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.36 The PBAC considered that the safety of sebelipase alfa was manageable.

### **Economic analysis**

- 6.37 The submission presented a cost utility analysis. Table 10 presents a summary of the model structure and rationale.
- 6.38 The economic evaluation base case and all the submission's sensitivity analyses resulted in incremental cost effectiveness ratios (ICER) that were extremely high (> \$1,055,000 per quality adjusted life year (QALY)). No plausible sensitivity analyses or alternative base cases could be specified for a conventionally acceptable ICER

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<sup>4</sup> Note that the HR calculation was conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

without a very substantial reduction in the price of sebelipase alfa. The submission acknowledged that “in all cases, the ICERs do not meet ‘usual’ cost-effectiveness thresholds.”

- 6.39 The submission base case included anniversary price reductions for sebelipase alfa every 5 years. The PBAC guidelines state, “Value future costs at current prices (ie do not allow for future inflation in the calculations), consistent with using constant prices in the economic evaluation”. Consequently, the evaluation presented a corrected base case and associated sensitivity analyses with the price reductions removed.

**Table 10: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost utility analysis
Outcomes	Life years, Quality adjusted life years
Time horizon	Life time (100 years) based on a median duration of follow-up of 241.7 weeks in LAL-CL03 and a median duration of follow up of 147.6 weeks in LAL-CL08.
Methods used to generate results	Markov Cohort analysis <sup>a</sup>
Health states	<p>Five health states are included in the model:</p> <ul style="list-style-type: none"> <li>• Infantile presentation LAL-D</li> <li>• Intensive care</li> <li>• General population QoL and survival</li> <li>• Natural mortality</li> <li>• LAL-D related mortality</li> </ul> <p>The submission considered natural mortality and LAL-related mortality to be separate states, whereas typically death is considered one absorbing health state. This presentation issue had no bearing model results.</p>
Cycle length	1 month. The submission stated that the economic model also factors in half-cycle corrections applied in the first cycle of the model, to reflect transitions occurring throughout the cycle. It was unclear if the application of the half cycle correction to the first cycle was appropriate, but a sensitivity analysis conducted during the evaluation indicated that this had almost no impact on the ICER.
Allocation to health states/ transition probabilities	Monthly mortality risk from LAL-D related causes and monthly mortality risk from non LAL-D related causes sourced from data in LAL-CL03, LAL-CL08 and LAL-1-NH01. See Figure 1.
Extrapolation	The submission assumed that patients who remain alive while on sebelipase alfa treatment after two years would have mortality consistent with the average Australian population. Likely optimistic.
Health related quality of life	<p>Utility values for patients in the 'Infantile presentation LAL-D' and 'Intensive care' health states are based on assumptions, and were the same values as used in the NICE model. Patients in 'Infantile presentation LAL-D' are assigned a utility score of 0.5 in this health state for the first 12 months of life, to reflect the stabilisation period. Patients who survived beyond 12 months of age remained in the 'Infantile presentation LAL-D' health state, however, they were assumed to have general population utility values from 12 months of age onwards, informed by McCaffery 2016. A utility score of 0.25 was estimated for patients in the 'Intensive care' health state, as per the NICE model. Patients who did not survive beyond 2 years of age progress from the 'Intensive care' health state.</p> <p>Australian general population utilities in the base case were based on McCaffrey 2016, which assessed health-related QoL norms measured using the EQ-5D-5L in a large, randomly selected community sample in South Australia. (N=2,908 adults). An alternative study (Clements 2014) was identified and used in a sensitivity analysis. The submission noted that neither study reported utility values in subjects aged under 15 years. Therefore, in the model it is assumed that patients aged under 15 years have the same utility as the 15-24 years age bracket.</p>
Software package	Excel 2010

Source: Table 3.1.1, p167 of the submission. LAL-D = Lysosomal acid lipase deficiency, NICE = National Institute for Health and Care Excellence

<sup>a</sup> The submission described the economic evaluation as a semi-Markov cohort analysis. It was unclear how this semi-Markov differed to a typical Markov analysis.

6.40 The submission stated that one-piece parametric extrapolation for survival in sebelipase alfa treated patients was explored, but that visual inspection showed that none of the parametric curves fit the LAL-CL03 data well, and consequently the submission did not consider parametric survival extrapolation appropriate in the sebelipase alfa arm. The submission stated that all patients in the LAL-1-NH01 dataset had died and as such parametric extrapolation was not considered in this arm.

- 6.41 Instead, the submission assumed that, for patients who respond to sebelipase alfa treatment (i.e. those who survive beyond 2 years), the treatment effect would be maintained for the duration of the model. The submission's approach to modelling long term survival for which there was no long term clinical data, was the most optimistic possible. A more conservative survival assumption may have been more reasonable. Moreover, as discussed in paragraph 6.25, data from LAL-CL03 and LAL-CL08 demonstrated that due to ADA development, the efficacy of sebelipase alfa could diminish in some patients. This suggested that there could be a plausible biological pathway for the efficacy of sebelipase alfa efficacy to wane over time.
- 6.42 Table 11 presents the key drivers of the model. The model was sensitive to the application of 'anniversary price reductions', discount rate, average dose of sebelipase alfa, and patient weight. The sensitivity of the model to these inputs was a reflection of the importance of drug acquisition costs in the model. The estimated undiscounted drug acquisition cost per patient was \$0 to < \$10 million in the first five years of life and \$20 million to < \$30 million from the ages of 17-21 years. While it was likely that the survival of patients treated with sebelipase alfa was a key driver of the model, as the submission's economic evaluation did not include operability to test alternative survival functions based on the parametric extrapolations, the impact could not be quantified during evaluation. The ESC noted the base case survival assumptions favoured sebelipase alfa substantially.
- 6.43 The evaluation noted that shortening the time horizon had the seemingly counterintuitive result of lowering the ICER. This, however, can be explained by the fact that incremental benefits, which stabilise after the first few years of the model, accrue more slowly than the incremental costs (which only increase as patients get older and require higher doses of sebelipase alfa).

**Table 11: Key drivers of the model**

Description	Method/Value	Impact (corrected base case ICER: \$ [redacted] <sup>1</sup> )
Survival extrapolation	The submission's base case assumed that all patients who survived at two years will have same mortality as the general population.	Unable to be quantified but likely high, favours sebelipase alfa. Model did not allow for testing with extrapolated functions or other survival assumption.
Average dose of sebelipase alfa	An average dose calculated for the first 2 years has been applied at a standard dose of 2.9 mg/kg once-a-week. After 2 years, patients are assumed to require 3.9 mg/kg once-a-week due to dose escalations. Comparatively, a maximum of 5 mg/kg was listed in the PI, and in the Global run registry for patients with LAL-D, 11/21 patients (52.4%) were using a dose that was listed as 'other' than 3 mg/kg (which could be >3 mg/kg), and dosages of up to 7.5 mg/kg have been used in LAL-CL08.	High, favours sebelipase alfa. Increasing the average dose of sebelipase alfa to 5 mg/kg increased the ICER by 25% to \$ [redacted] <sup>1</sup> /QALY
Patient weight	Baseline median WFA percentiles were observed in the 2 <sup>nd</sup> percentile in LAL-CL03 and LAL-CL08, therefore the model assumed that patients will be in the 3 <sup>rd</sup> WFA percentile in the first year on treatment with sebelipase alfa according to World Health Organization growth charts. The submission stated that Global LAL-D Registry data had demonstrated that patients on long-term sebelipase alfa therapy have most commonly been in the 25 <sup>th</sup> WFA percentile, which was used to form the basis of the calculated cost of sebelipase alfa from Year 2 onwards. This resulted in a maximum weight of 58.3kg in the model. Comparatively, ABS data <sup>5</sup> indicated that in 2017-18, the average Australian male weighed 87 kg and the average Australian female weighed 72kg	Moderate. Setting patient weight to the 50 <sup>th</sup> WHO WFA percentile increased the ICER by 9% to \$ [redacted] <sup>1</sup> /QALY

Source: pp184-194 of the submission. ICER = incremental cost effectiveness ratio. WFA = weight for age

The redacted values correspond to the following ranges:

<sup>1</sup> > \$1,055,000

6.44 Table 12 presents the results of the stepped economic evaluation.

<sup>5</sup> <https://www.abs.gov.au/articles/how-healthy-typical-australian>

**Table 12: Results of the stepped economic evaluation**

Step and component	Sebelipase alfa	BSC	Increment
<b>Step 1: cost per life year gained 5 year time horizon</b>			
Costs	\$ <sup>1</sup>	\$144,066	\$ <sup>1</sup>
LY	3.18	0.30	2.89
Incremental cost/extra LY gained			\$ <sup>1</sup>
<b>Step 2: cost per life year gained time horizon 10 years</b>			
Costs	\$ <sup>1</sup>	\$144,066	\$ <sup>1</sup>
LY	5.56	0.30	5.26
Incremental cost/extra LY gained			\$ <sup>1</sup>
<b>Step 3: Cost per QALY 10 year time horizon</b>			
Costs	\$ <sup>1</sup>	\$144,066	\$ <sup>1</sup>
QALY	4.96	0.13	4.83
Incremental cost/extra QALY gained			\$ <sup>1</sup>
<b>Step 4: Cost per QALY lifetime time horizon</b>			
Costs	\$ <sup>1</sup>	\$144,066	\$ <sup>1</sup>
QALY	12.73	0.13	12.60
Incremental cost/extra QALY gained			\$ <sup>1</sup>
<b>Corrected base case (no anniversary price reductions)</b>			
Costs	\$ <sup>1</sup>	\$144,066	\$ <sup>1</sup>
QALY	12.73	0.13	12.60
Incremental cost/extra QALY gained			\$ <sup>1</sup>

Source: Table 3.8.2, p191 of the submission. BSC = best supportive care; LY= life year; QALY = quality adjusted life year.

The redacted values correspond to the following ranges:

<sup>1</sup> > \$1,055,000

- 6.45 Overall, the ICER was extremely high in all steps of the economic evaluation, and likely to be underestimated given the highly optimistic assumptions around survival and weight of patients as well as the application of ‘anniversary price reductions’ to sebelipase alfa pricing and the dosage of sebelipase assumed.
- 6.46 The majority of the incremental life years and QALYs gained were attributable to the assumption that patients treated with sebelipase alfa will achieve quality of life and survival consistent with that of the general population. The ESC considered the assumption that patients treated with sebelipase alfa have a normal life expectancy if they survive to 24 months and the application of general population utilities beyond 12 months of age was highly optimistic and the most favourable assumption for sebelipase alfa.
- 6.47 Table 13 presents the results of sensitivity analyses around the economic evaluation.

Table 13: Results of the corrected sensitivity analyses

Description	Incremental cost (\$)	Incremental QALY	ICER (\$)	% Change
Corrected base case	1	12.60	1	-
'Anniversary price reduction' applied (submission base case)	1	12.60	1	-27.55%
Average dose of sebelipase alfa 3.33 mg/kg	1	12.60	1	-15.47%
Average dose of sebelipase alfa 5 mg/kg	1	12.60	1	25.20%
Patient weight 50 <sup>th</sup> WHO WFA percentile	1	12.60	1	9.25%
Include societal perspective (include cost of productivity loss due to early mortality)	1	12.60	1	-4.13%
Use utilities from Clemens 2014	1	12.00	1	5.03%
Time horizon shortened to 50 years	1	11.79	1	-4.17%
Time horizon shortened to 1 year	2	0.13	1	-73.64%

Source: Table 3.9.1, p194 of the submission. BSC= best supportive care; HSCT = haematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; QALY= quality-adjusted life years; WFA, = weight-for-age; WHO = World Health Organization

The redacted values correspond to the following ranges:

<sup>1</sup> > \$1,055,000

<sup>2</sup> \$155,000 to < \$255,000

6.48 The submission concluded that given the ultra-rare nature of infantile onset LAL-D, the cost of sebelipase alfa should be balanced against the significant survival benefits and the high unmet clinical need for therapies that reverse the course of disease and ultimately saves lives. The submission considered that the cost-effectiveness results should be viewed in this context. The PSCR stated the sponsor intends to apply for inclusion of sebelipase alfa on the life-saving drug program (LSDP), if the PBAC accepts that sebelipase alfa is clinically effective but not cost effective for listing on the Pharmaceutical Benefits Scheme.

### Drug cost/patient/year

6.49 Treatment with sebelipase alfa is expected to be life-long. The economic evaluation estimated a total lifetime cost per patient of \$200 million to < \$300 million (assuming no anniversary price reductions) based on a vial price of \$1 and an expected total lifetime use of 30,000 to < 40,000 vials (estimated through back-calculation during the evaluation). In contrast, the financial estimates (calculating costs over the first six years of listing) estimated a total cost of \$0 to < \$10 million for first 6 years of listing based on an average of 500 to < 5,000 vials used per patient over the first 6 years of listing. These differences were not only driven by the time horizon but also by the expected weight change based on age and consequently the cumulative dose of sebelipase alfa. The financial estimates only calculate estimates for patients aged 0-7 years, whereas the economic evaluation calculates doses throughout an entire lifetime. For context, the estimated drug acquisition cost per patient was \$0 to < \$10 million in the first 5 years of life and \$20 million to < \$30 million from the ages of 17-21 years.

6.50 Table 14 presents the calculations of cost per patient per course.

**Table 14: Drug cost per patient for sebelipase alfa**

	Trial dose and duration		Model	Financial estimates
Mean dose	LAL-CL03	Starting dose of 0.35 mg/kg once-a-week, dose escalated to 1 mg/kg once-a-week, then 3 mg/kg once-a-week and then 5 mg/kg once-a-week were allowed.	2.9 mg/kg/ years 1&2 3.9 mg/kg after	
	LAL-CL08	Sebelipase alfa starting dose of 1 mg/kg once-a-week, dose escalated to 3 mg/kg once-a-week, then 5 mg/kg once-a-week and then 7.5 mg/kg once-a-week were allowed.		
Mean duration	LAL-CL03 median 241.7 weeks LAL-CL08 median 147.6 weeks		Lifetime	6 years
Total number of vials	Not reported		a1	b4
Cost per vial			\$	
Cost/patient/course	Not calculable <sup>d</sup>		\$ <sup>2</sup> (no price reductions) \$ <sup>3</sup> (assuming anniversary price reductions.	\$ <sup>5</sup> for first 6 years of listing <sup>c</sup>

Source: sebelipase alfa economic model.xlsx, sebelipase alfa BIM.xlsx and Table 2.4.12, p87 of the submission.

<sup>a</sup> back calculated during the evaluation by dividing total undiscounted lifetime drug acquisition cost ( assuming no anniversary price reductions) by vial price

<sup>b</sup> Back-calculated during the evaluation by dividing the total PBS cost over the 6 years of listing the vial price (and the dividing by the number of patients (4)

<sup>c</sup> Calculated during the evaluation by dividing the total PBS costs over the first 6 years of listing by the number of patients (4).

<sup>d</sup> A cost per patient could not be calculated because the submission and attached CSRs did not give detailed enough dosing data to estimate number of vials used per patient.

The redacted values correspond to the following ranges:

<sup>1</sup> 30,000 to < 40,000

<sup>2</sup> \$200 million to < \$300 million

<sup>3</sup> \$100 million to < \$200 million

<sup>4</sup> 500 to < 5,000

<sup>5</sup> \$0 to < \$10 million

### **Estimated PBS usage & financial implications**

6.51 This submission was considered by DUSC. The submission used an epidemiological approach to estimating use.

6.52 Table 15 presents the key inputs and data sources used to estimate financial impact.

**Table 15: Data sources and parameter values applied in the utilisation and financial estimates**

Data	Value	Source	Comment
<b>Eligible population</b>			
Incidence rate	1/704,000	Meikle et al 1999	<p>The incidence rate was estimated from retrospective data on enzymatic diagnosis from patient referrals and prenatal diagnoses for the period of Jan 1, 1980, to Dec 31, 1996 in the two centres for which the data was collect represented all enzymatic analyses performed in Australia during that time.</p> <p>Meikle 1999's estimate of LAL-D (Wolman's disease) were based on a very low number of diagnoses over the 16 years analysed (n=8), and no confidence intervals were presented in the estimates of incidence. The median age of diagnosis reported was 0.6 years, and that the maximum age of diagnosis was 5.5 years, which was inconsistent with the evidence with LAL-1-NH01 and in the economic evaluation which suggested no patient with LAL-D survived to 5 years with BSC alone.</p> <p>It was noted during the evaluation that the NICE appraisal for sebelipase alfa stated, "The estimated incidence of LAL deficiency is 1 in 500,000 to 1 in 1,000,000 in children presenting in infancy." (p4, NICE ID 737). This was reasonably consistent with the Meikle 1999 estimate.</p>
<b>Treatment utilisation</b>			
Uptake rate	100%	Assumption	Reasonable given the severity of the condition and the absence of other options.
Probability discontinuation during Year 1 and Year 2	0%	Assumption.	Six out of 19 (31.5%) total patients died in LAL-CL03 and LAL-CL08 in the first two years but the financial estimates assumed all patients treated with sebelipase alfa will survive. Given the very low estimated population in the first six years of listing, assuming no discontinuation may not be conservative as it was impossible to estimate fractional patients, unlike a cohort level estimate.
<b>Costs</b>			
EMP for sebelipase alfa	\$	Requested price	Consistent with the corrected base case economic model.
Dose	<p>2.9 mg/kg once week for the first 2 years. After 2 years, 3.9 mg/kg once per week.</p> <p>Patient weight 25<sup>th</sup> WFA percentile.</p>	LAL-CL03 and LAL-CL08	<p>In LAL-CL03, patients used a starting dose of 0.35 mg/kg once-a-week before the dose was escalated to 1 mg/kg once-a-week. In LAL-CL08, sebelipase alfa was able to be titrated up to 7.5 mg/kg once-a-week. The DUSC noted there was substantial variation in dose escalation and titration endpoints between the studies and considered the submission's calculation of average dose was uncertain.</p>

Source: Tables 4.1.1 and 4.1.2, p198 of the submission. EMP = ex-manufacturer price; DPMQ = dispensed price per maximum quantity kg = kilogram; MBS = Medicare Benefits Schedule; mg = milligram; PBS = Pharmaceutical Benefits Scheme

6.53 Table 16 summarises the estimated use and financial implications.

**Table 16: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Australian births per year	310,231	310,648	311,065	311,481	311,898	312,315
Incidence rate	1/704,000 births					
Incident population	1	0	1	0	1	0
Accumulated eligible population <sup>a</sup>	2	2	3	3	4	4
<b>Number of units dispensed<sup>a</sup></b>						
Grandfathered patient	1	1	1	1	1	1
Patient 1						
Patient 2						
Patient 3						
Total	1	1	1	1	3	3
<b>Estimated financial implications of sebelipase alfa<sup>b</sup> (\$)</b>						
Grandfathered patient	2	2	2	2	2	2
Patient 1	2	2	2	2	2	2
Patient 2	\$0	\$0	2	2	2	2
Patient 3	\$0	\$0	\$0	\$0	2	2
Net cost to PBS	2	2	2	2	2	2
<b>Net financial implications (\$)</b>						
Net cost to PBS	2	2	2	2	2	2
Net cost to MBS	2	2	2	2	2	2
<b>Net cost to Government</b>	2	2	2	2	2	2

Source: Tables 4.2.1 – 4.2.5, pp200-204 and Tables 4.5.3- 4.5.3, p206 of the submission.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule

<sup>a</sup> Assuming 2.9 mg/kg dose in Year 1, then 3.9 mg/Kg dose after and weight for age (WFA dosing) described in Section 3 and 4.

<sup>b</sup> based on a requested vial price of \$█

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

<sup>3</sup> 500 to < 5000

- 6.54 The submission estimated that one grandfathered patient and three incident patients would be treated with sebelipase alfa over the first six years of listing.
- 6.55 The submission estimated that the net cost to government would be \$0 to < \$10 million in Year 1 increasing to \$0 to < \$10 million in Year 6, for a total of \$20 million to < \$30 million over the first six years of listing.
- 6.56 The DUSC considered the estimates presented in the submission to be underestimated. The main issues were:
- The drug cost per patient varies greatly based on weight and age. As the cumulative number of patients would be expected to increase, and continuing patients would have a higher weight as they get older, the financial impact of the first six years of listing was a poor indicator of the total costs expected with treatment with sebelipase alfa. For example, the net cost for listing in the first six years was estimated to be \$20 million to < \$30 million (for four patients), but a sensitivity analysis conducted during the evaluation considering a further six years of listing estimated costs of \$70 million to < \$80 million (for seven patients) for years 7-12 of listing.

- The restriction (as proposed in Section 3) did not define an age limit (only specifying “infant”). There is potential for use outside the proposed restriction to older children and adults, as sebelipase alfa is TGA registered for the long-term treatment of patients of all ages with LAL-D. The restriction did not specify a maximum dose. There is a potential for patients with ADAs requiring a higher dose.
- The average dose/age and average weight/age calculated in the submission were likely underestimated, when compared to the LAL-CL03 and LAL-CL08 trial data.
- The costs associated with using haematopoietic stem cell transplants to treat patients with ADAs (whole gene deletions) were not included in the financial estimates.

6.57 The pre-PBAC response provided a sensitivity analysis which assumed all patients will receive 5 mg/kg once-a-week from 1 year of age and will weigh in the 50th WHO WFA percentile which increased the net cost over 6 years from \$20 million to < \$30 million to \$30 million to < \$40 million .

### **Quality Use of Medicines**

6.58 The submission noted that the sponsor was committed to the Quality Use of Medicines (QUM) through implementation of TGA approved label wording and consumer medicines information.

6.59 The submission also noted that a Global LAL-D registry has been established and forms part of the sponsor’s pharmacovigilance activities.

6.60 The submission stated that the Global LAL-D registry was established for the purpose of understanding the disease, its progression, associated complications and to evaluate the long-term effectiveness and safety of sebelipase alfa.

### **Financial Management – Risk Sharing Arrangements**

6.61 The submission did not propose a risk sharing arrangement.

*For more detail on PBAC’s view, see section 7 PBAC outcome*

## **7 PBAC outcome**

7.1 The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) listing of sebelipase alfa for the treatment of infantile onset lysosomal acid lipase deficiency (LAL-D). The PBAC considered sebelipase alfa was an effective treatment for infantile onset LAL-D; however, the incremental cost effectiveness ratio (ICER) for sebelipase alfa compared to best supportive care was extremely high and uncertain.

7.2 The PBAC noted the consumer comment received for this item was supportive of making sebelipase alfa available for infants with this very rare condition. The PBAC noted the health care professional that provided a consumer comment had also

successfully treated an adolescent patient with cholesteryl ester storage disease (CESD) with sebelipase alfa, which is not the subject of this submission.

- 7.3 The PBAC noted the submission nominated best supportive care (defined as nutritional support, blood transfusions, steroids and lipid-lowering treatments) as the comparator and considered this was reasonable. The PBAC noted the prognosis for patients with infantile onset LAL-D treated with best supportive care is generally poor with none surviving beyond 12 months of age.
- 7.4 The PBAC noted the limitation of the clinical data in this rare disease. The PBAC noted the submission presented results from two single-arm, open-label studies of sebelipase alfa (LAL-CL03, n= 9 and LAL-CL08, n=10) and a subgroup of untreated patients with early growth failure from a natural history study (n=21). The PBAC noted that 79% of patients treated with sebelipase alfa survived to 12 months and 68% of patients survived to 24 months, compared to none in the natural history study. The PBAC noted sebelipase alfa increased median weight for age percentiles and length or height for age percentiles compared to a decrease in these outcomes in patients in the natural history study.
- 7.5 The PBAC noted 10/19 patients treated with sebelipase alfa developed anti-drug antibodies (ADAs), with the development of high-titre ADAs found to correlate with reduced clinical response to treatment. The PBAC noted patients with high-titre ADAs and loss of efficacy required an increase in sebelipase alfa dose (including to doses higher than 5 mg/kg) and other clinical measures including the addition of immunomodulatory therapy and HSCT or bone marrow transplants. The PBAC noted the development of high-titre ADAs may be associated with the deletion of the entire *LIPA* gene which was observed in 3/19 patients in the clinical studies.
- 7.6 The PBAC noted all patients experienced treatment emergent adverse events (TEAE) with the most common events including diarrhoea, vomiting and pyrexia. The PBAC noted infusion-associated reactions occurred in 13/19 (68%) of patients and may have been more common in patients with the development of ADA. The PBAC noted no patient withdrew from the studies due to TEAEs and considered that, overall, the safety of sebelipase alfa was manageable.
- 7.7 The PBAC noted the cost of treating patients with sebelipase alfa over a lifetime was very uncertain with costs likely to be higher than estimated in the submission due to weight gain by patients, due to an initial improvement in weight for age percentiles, increasing age and increasing dose due to waning response. The PBAC noted this had a significant impact on the cost effectiveness of sebelipase alfa and the financial implications of listing on the PBS for infantile LAL-D.
- 7.8 The PBAC noted the corrected base case ICER was > \$1,055,000/ QALY and considered this was likely to be underestimated as the base case assumptions were highly optimistic and favoured sebelipase alfa (refer to paragraph 6.46). The PBAC

acknowledged a reasonable scenario whereby sebelipase alfa was cost-effective for infantile onset LAL-D was not able to be determined.

- 7.9 The PBAC agreed with the DUSC that the financial estimates provided in the submission were underestimated for the reasons outlined in paragraph 6.56. The PBAC considered the financial estimates (over 6 years) did not accurately represent the opportunity cost of listing sebelipase alfa on the PBS as it reflected the cost of treating 4 patients up to a maximum of 6 years of age and the cost per patient would increase substantially as a patient ages and their weight increases. The PBAC also considered that the financial estimates were highly uncertain, as they were based on an assumption that one new patient would be added every 2.3 years, but this was inherently highly uncertain (e.g. it is plausible that the number of new patients added could be much higher or lower due to chance). The PBAC noted that no RSA was proposed to share this risk.
- 7.10 The PBAC considered the following additional changes to the restriction criteria would be appropriate in a resubmission:
- Deletion of the clinical criteria: ‘The condition must have documented abnormalities in the lysosomal acid lipase (LAL) gene’;
  - Addition of the clinical criteria: ‘(i) The condition must be diagnosed by leukocyte-based assay with or without genetic testing and (ii) The condition must have a residual LAL enzyme activity of less than 1%’.
  - The clinical criteria regarding a diagnosis in infancy should specify diagnosis of LAL-D in infants under 12 months of age;
  - The Prescribing Instructions should specify a maximum dose of 5 mg/kg.
- 7.11 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Alexion welcomes the PBAC's acknowledgment that sebelipase alfa is an effective treatment for infantile onset LAL-D, an ultra-rare disease. We will continue to pursue funding for this life-saving medicine where there are no alternative therapies available.