7.6 TALIGLUCERASE ALFA powder for IV infusion, 200 units; Elelyso®; Pfizer Australia Pty Ltd.

1 Purpose of Application

1.1 The major resubmission sought PBS listing as a Section 100 (Highly Specialised Drugs Program) benefit for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Type 1 Gaucher disease.

2 Requested listing

2.1 The requested listing is shown below with Secretariat suggestions shown in *italics* (additions) and ~~strikethrough~~ (deletions):

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
TALIGLUCERASE ALFA 200 units injection, 1 vial	1	0	Elelyso® PZ

Category / Program	Section 100 – Highly Specialised Drugs Program (Private Hospital) Section 100 – Highly Specialised Drugs Program (Public Hospital)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	---
Severity:	---
Condition:	*Type 1 Gaucher Disease*
PBS Indication:	~~Long-term enzyme replacement therapy for adult and paediatric patients with a confirmed diagnosis of~~ Type 1 Gaucher disease
Restriction level / Method:	☐*Restricted benefit* ☒*Authority Required - In Writing* ☒*Authority Required - Telephone* ☒*Authority Required – Emergency* ☒*Authority Required - Electronic* ☐*Streamlined*
Treatment criteria:	*Must be treated by a metabolic physician*
Clinical criteria:	The condition ~~may~~ *must* include one or more of ~~the following:~~ splenomegaly, hepatomegaly, anaemia or thrombocytopenia.

Prescriber Instructions	*Clinical criteria are defined as:* - *Haemoglobin ≤ 105 g/L for females and ≤115 g/L for males on at least 2 occasions more than 1 month apart* - *Platelet count ≤ 120 x 10^9 /L on at least 2 occasions more than 1 month apart* - *Liver volume 1.25 times normal (CT or MRI)* - *Spleen volume 5 times normal (CT or MRI).*
Administrative Advice	*NOTE:* *Increased maximum quantities should be based on a dosing regimen of 30 to 60 units/kg every 2 weeks to provide sufficient supply for one month treatment* *NOTE:* *Increased number of repeats may be requested up to a maximum of five repeats.*

3 Background

3.1 Taliglucerase alfa was TGA registered on 21 May 2014 as a long-term enzyme replacement therapy for adult and paediatric patients with a confirmed diagnosis of Type 1 Gaucher disease associated with at least one of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopaenia.

3.2 This drug has had one previous consideration by the PBAC in March 2012.

3.3 In March 2012, the PBAC rejected the submission on the basis of uncertain clinical effectiveness, unknown equi-effective doses and unknown interchangeability.

4 Clinical place for the proposed therapy

4.1 Gaucher disease is a rare, inherited condition caused by mutations in the human glucocerebrosidase gene leading to reduced activity of the lysosomal enzyme glucocerebrosidase and the accumulation of substrate glucocerebrosidase in the cells of the monocyte-macrophage system. This accumulation leads to the visceral manifestations of hepatosplenomegaly (enlarged spleen and liver), anaemia and thrombocytopenia, skeletal features and less frequently lung involvement. Gaucher disease is typically classified according to the existence and severity of neuronopathic involvement.

4.2 The resubmission positioned taliglucerase alfa as an equivalent alternative enzyme replacement therapy to imiglucerase and velaglucerase alfa for the treatment of Type 1 Gaucher disease.

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

5 Comparator

5.1 The resubmission nominated imiglucerase and velaglucerase alfa. Imiglucerase was the nominated comparator in the previous submission. Velaglucerase alfa had been added as an additional comparator in the resubmission since it had become available in Australia since the first submission. The ESC considered this appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 All previous studies in the first submission with updated data (where available) were presented along with one new non-randomised Australian study, and five randomised and non-randomised velaglucerase alfa studies.

6.4 No direct randomised trials comparing taliglucerase alfa with imiglucerase or velaglucerase alfa were identified in the literature search. There were no trials comparing these treatments to placebo that would allow a formal indirect comparison. The ESC noted that the resubmission relied heavily on a small Australian case series (n=11) and advised that this naïve indirect comparison was likely to only be supportive. The pre-PBAC response (p1) contended that the case series presented informative primary evidence of real-world data on the safety and efficacy of taliglucerase alfa in the Australian population.

6.5 The submission was based on 8 randomised trials and 9 non-randomised studies as follows:

Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Taliglucerase alfa randomised trials		
PB-06-001	Protalix clinical study report (September 2009). A Phase III Multicenter, Randomized, Double-Blind Trial to Assess the Safety and Efficacy of Two Parallel Dose Groups of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients with Gaucher Disease.	Internal study report, September 2009
	Zimran et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease.	*Blood* 2011; 118(22): 5767-5773
	Zimran et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease (erratum).	*Blood* 2012; 119(19): 4577
	Aviezer et al. Novel enzyme replacement therapy for Gaucher disease: phase III pivotal clinical trial with plant cell expressed recombinant glucocerebrosidase (prGCD) - taliglucerase alpha.	*Molecular Genetics and Metabolism.* 2010 Conference: 6th Annual Research Meeting of the Lysosomal Disease Network's, WORLD Symposium 2010 Miami, FL

		United States. Conference Publication; 99(2):S9-S10.
	Aviezer et al. Novel enzyme replacement therapy for Gaucher disease: ongoing phase III clinical trial with recombinant human glucocerebrosidase expressed in plant cells.	*Molecular Genetics and Metabolism.* 2009 Conference: 4th Lysosomal Disease Network's We're Organizing Research on Lysosomal Diseases (WORLD) Symposium 2009 Las Vegas, NV United States. Conference Publication: 96 (2):S13-S14.
PB-06-005 [a]	Protalix clinical study report. A multicenter, double-blind, randomized safety and efficacy study of two dose levels of taliglucerase alfa in pediatric subjects with Gaucher disease.	Internal study report, January 2014
	Zimran et al. A multicenter, double-blind, randomized safety and efficacy study of two dose levels of taliglucerase alfa in pediatric patients with Gaucher disease.	*Molecular Genetics & Metabolism* 2013; 108(2): Abs264.
	Zimran et al. A multicenter, double-blind, randomized safety and efficacy study of two dose levels of taliglucerase alfa in pediatric patients with Gaucher disease.	*Blood* 2012 Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. Conference Publication: 120(21); 2140.
Taliglucerase alfa non-randomised studies		
PB-06-002	Protalix clinical study report. A Phase 3 Multicenter, Open-label, Switchover Trial to Assess the Safety and Efficacy of Plant Cell Expressed Recombinant Human Glucocerebrosidase (Taliglucerase alfa) in Patients with Gaucher Disease Treated with Imiglucerase (Cerezyme®) Enzyme Replacement Therapy	Internal study report, May 2013
	Pastores et al. Plant cell expressed recombinant glucocerebrosidase - taliglucerase alfa as therapy for Gaucher disease in patients previously treated with imiglucerase.	*Molecular Genetics & Metabolism* 2012; 105(2): S50.
PB-06-003	Protalix clinical study report interim analysis. A multicenter extension trial of plant cell expressed recombinant human glucocerebrosidase (taliglucerase alfa) in patients with Gaucher Disease.	Internal study report, May 2012
	Zimran et al. Long term safety and efficacy data of taliglucerase alfa, a plant cell expressed recombinant glucocerebrosidase, in treatment of naïve Gaucher disease patients.	*Molecular Genetics & Metabolism* 2012. Conference: 8th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium 2012 San Diego, CA United States. Conference Publication; 105(2): S68
PB-06-004 [d]	Protalix clinical study report. An open-label expanded access trial of plant cell expressed recombinant human glucocerebrosidase (prGCD) in patients with Gaucher disease who require enzyme replacement therapy.	Internal study report, December 2013
PB-06-006 [b,c]	Protalix clinical study protocol. A multicenter extension study of taliglucerase alfa in pediatric subjects with Gaucher disease.	Internal study protocol, October 2012
	Protalix pharmacokinetic report. A multicenter extension study of taliglucerase alfa in pediatric subjects with Gaucher disease – a protocol amendment to evaluate pharmacokinetics of taliglucerase	Internal pharmacokinetic report, July 2013

	alfa in pediatric subjects.	
Szer 2014 [b]	Taliglucerase: The Australian Experience	Unpublished abstract
Imiglucerase randomised trials		
HGT-039	Ben Turkia et al. Velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease.	*American Journal of Hematology* 2013; 88(3):179-84.
Elstein 2007	Elstein et al. Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement.	*Blood* 2007; 110(7):2296-2301.
de Fost 2007	de Fost et al. Low frequency maintenance therapy with imiglucerase in adult type I Gaucher disease: a prospective randomized controlled trial.	*Haematologica* 2007; 92(2): 215-221.
Schiffmann 2002	Schiffmann et al. Decreased bone density in splenectomized Gaucher patients receiving enzyme replacement therapy.	*Blood Cells, Molecules, and Diseases* 2002: 28(2);288-296.
Grabowski 1995	Genzyme Corporation. Protocol RC 91-0110: An Evaluation of the Safety and Effectiveness of Recombinant, Human, Macrophage-Targeted β-Glucocerebrosidase	Genzyme clinical research website, 2005
	Genzyme Corporation. Protocol RC 92-0501: An extended evaluation of the safety and effectiveness of recombinant, human-derived, macrophage-targeted β glucocerebrosidase in patients with Gaucher disease.	Genzyme clinical research website, 2005
	Grabowski et al. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources.	*Annals of Internal Medicine* 1995; 122(1):33-39.
Imiglucerase non-randomised studies		
Sims 2008	(Clinical trial Number: NCT00365131) Sims et al. Improvement of bone disease by imiglucerase (Cerezyme) therapy in patients with skeletal manifestations of type 1 Gaucher disease: results of a 48-month longitudinal cohort trial.	Clinical Genetics 2008; 73:430-440.
Velaglucerase alfa randomised trials		
TKT-032 [b]	NCT00430625. A multicenter, randomized, double-blind, parallel group, two-dose study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) enzyme replacement therapy in patients with type 1 Gaucher disease.	Clinical trial registry
	Zimran et al. Enzyme replacement therapy with velaglucerase alfa significantly improves key clinical parameters in type 1 Gaucher disease: Positive results from a randomized, double-blind, global, phase III study.	*Molecular Genetics & Metabolism* 2010. Conference: 6th Annual Research Meeting of the Lysosomal Disease Network's, WORLD Symposium 2010 Miami, FL United States. Conference Publication; 99 (2):S41.
	Zimran et al. Enzyme replacement therapy with velaglucerase alfa improves key clinical parameters in a pediatric subgroup with type 1 Gaucher disease.	*Molecular Genetics & Metabolism* 2010 Conference: 6th Annual Research Meeting of the Lysosomal Disease Network's, WORLD Symposium 2010 Miami, FL United States. Conference Publication; 99(2):S40-S41.
	Gonzales et al. Clinically significant haemoglobin response observed within 3 months following treatment with velaglucerase alfa in patients with type 1 Gaucher disease.	*Journal of Inherited Metabolic Disease* 2010 Conference: Annual Symposium of the

		Society for the Study of Inborn Errors of Metabolism Istanbul Turkey. Conference Publication; 33:S139.
	Zimran et al. Enzyme replacement therapy with velaglucerase alfa significantly improves key clinical parameters in type 1 Gaucher disease: positive results from a randomized, double-blind, global, phase III study.	*Haematologica* 2010 Conference: 15th Congress of the European Hematology Association, EHA 2010 Barcelona Spain. Conference Publication; 95:75-76.
Velaglucerase alfa non-randomised studies		
TKT-034 [b]	NCT00478647. Study of GA-GCB enzyme replacement therapy in type 1 Gaucher disease patients previously treated with imiglucerase.	Clinical trial registry
	Zimran et al. Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase.	*American Journal of Hematology* 2013; 88(3):172-8.
	Pastores et al. Safety and efficacy of velaglucerase alfa in patients with type 1 Gaucher disease previously treated with imiglucerase: ongoing extension of study TKT034.	*Journal of Inherited Metabolic Disease* 2010; 33(Suppl. 1): S130.
	Grabowski et al. Safety and efficacy of velaglucerase alfa in patients with Gaucher disease type 1 previously treated with imiglucerase: 1-year, multicenter, phase III clinical trial.	*Haematol-Hematol. J*. 2010; 95: Abs 0191, Suppl. 2.
	Grabowski et al. Safety and efficacy of velaglucerase alfa in patients with Gaucher disease type 1 previously treated with imiglucerase: 1-year, multicenter, phase III clinical trial.	*Haematologica* 2010. Conference: 15th Congress of the European Hematology Association, EHA 2010 Barcelona Spain. Conference Publication; 95:77.
TKT-025/TKT-025 Ext [b]	NCT00391625. Open-label extension study evaluating long term safety in patients with type 1 Gaucher disease receiving DRX008A (ERT).	Clinical trial registry
	Zimran et al. Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience.	*Blood* 2010; 115(23):4651-6.
	Elstein et al. Early achievement and maintenance of the therapeutic goals using velaglucerase alfa in type 1 Gaucher disease.	*Blood Cells Molecules & Diseases* 2011; 46(1):119-23.
	Elstein et al. Significant and continuous improvement in bone mineral density among type 1 Gaucher disease patients treated with velaglucerase alfa: 69-month experience, including dose reduction.	*Blood Cells Molecules & Diseases* 2011; 47(1): 56-61.
	Elstein et al. A 7-year open-label study of clinical parameters and therapeutic goals in patients with type 1 Gaucher disease receiving treatment with velaglucerase alfa: Updating the long-term experience with velaglucerase alfa.	*Molecular Genetics & Metabolism* 2013 108(2): S37.
	Zimran et al. Safety and efficacy of velaglucerase alfa in patients with type 1 Gaucher disease: 2 years of treatment in phase III trials and an extension study.	*Molecular Genetics & Metabolism* 2012. Conference: 8th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium 2012 San Diego, CA United States. Conference Publication; 105(2):S69.
	Elstein et al. Achievement of therapeutic goals over 2 years of velaglucerase alfa enzyme replacement therapy in patients with type 1 Gaucher disease.	*Molecular Genetics & Metabolism* 2012. Conference: 8th Annual

		Research Meeting of the Lysosomal Disease Network, WORLD Symposium 2012 San Diego, CA United States. Conference Publication; 105(2):S28.
	Crombez et al. Two-year efficacy and safety of velaglucerase alfa in patients with type 1 Gaucher disease switching from imiglucerase: Phase III trial HGT-GCB-039 and extension.	*Molecular Genetics & Metabolism* 2012. Conference: 8th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium 2012 San Diego, CA United States. Conference Publication; 105(2):S25-S26.
	Ben Turkia et al. Achievement of therapeutic goals in patients with type 1 Gaucher disease (GD1) on velaglucerase alfa or imiglucerase: Phase III trial HGT-GCB-039 and extension.	*Journal of Inherited Metabolic Disease* 2011. Conference: Annual Symposium of the Society for the Study of Inborn Errors of Metabolism 2011 Geneva Switzerland. Conference Publication; 34:S224.
	Elstein et al. Bone mineral density in adults with type 1 Gaucher disease receiving velaglucerase alfa 60U/kg every other week: 2-year results.	*Journal of Inherited Metabolic Disease* 2012; 35(Suppl. 1): S150.
HGT-044 [b,d]	NCT00635427. An Open-label extension study of GA-GCB ERT in patients with type 1 Gaucher disease.	Clinical trial registry
	Mehta et al. Two-year safety and tolerability of velaglucerase alfa in patients with type 1 Gaucher Disease, including patients switched from imiglucerase: phase III Trial HGT-GCB-039 and extension.	*Blood* 2011. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States. Conference Publication; 118(21):Abs3214.

[a] Data updated from previous submission
[b] New data to resubmission
[c] Study ongoing, no efficacy data available
[d] Safety only
Source: Table 4, Table 5, Table 6, ppB.18-B.22 of the submission

6.6 The key features of the randomised and non-randomised trials are summarised in the table below. The ESC noted the small number of patients in each trial as well as the high risk of bias in the non-randomised studies.

Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Primary outcomes (Change from baseline)
Taliglucerase alfa randomised trials					
PB-06-001	31	R, DB, PG, MC 9 mths	Low	Treatment-naïve adults	Spleen volume
PB-06-005	11	R, DB, PG, MC 12 mths	Low	Treatment-naïve paediatric	Haemoglobin

Trial	N	Design/duration	Risk of bias	Patient population	Primary outcomes (Change from baseline)
Taliglucerase alfa non-randomised trials					
PB-06-002	31	OL, MC, switching 9 mths	High	Adults and children previously stabilised on imiglucerase	Clinical deterioration
PB-06-003	44	Ext. PB-06-001 /PB-06-002 15-30 mths	High	Adults with previous taliglucerase treatment	No specific outcomes
PB-06-004	36	OL expanded access program Up to 33 mths	High	Adults historically treated with imiglucerase	Haemoglobin and platelet counts, biomarkers
PB-06-006 (ongoing)	15	Ext. PB-06-005 /PB-06-002 Up to 24 months	High	Paediatric patients with previous taliglucerase treatment	Spleen and liver volume, platelets, haemoglobin, biomarkers
Szer 2014	11	Retrospective, descriptive review	High	Australian patients previously stabilised on imiglucerase	Platelets, haemoglobin, biomarkers, bone marrow burden
Imiglucerase randomised trials					
HGT-039	34	DB, R, MC 9 mths	Low	Treatment naïve adult and paediatric	Haemoglobin
Elstein 2007	36	OL, R, PG 6 mths	High	Adults previously stabilised on imiglucerase	Spleen / liver volume, haemoglobin, platelets
De Fost 2007	11	OL, R, dose frequency 12 months	High	Adults previously stabilised on imiglucerase	Low vs standard frequency dosing: change in liver ratio
Schiffmann 2002	29	DB, R 24 mths	Low	Splenectomised, treatment-naïve adults	Bone mineral density of lumbar spine
Grabowski 1995	30	DB, R, PG 9 mths	Low	Treatment naïve adult and paediatric	Haemoglobin, platelets, liver and spleen volumes, IgG antibodies
Imiglucerase non-randomised study					
Sims 2008	33	OL, MC, safety 48 mths	High	Adult and paediatric (≥10yrs) treatment naïve w/ history of bone disease problems	Improvement in bone pain, bone crises and bone mineral density
Velaglucerase alfa randomised trial					
HGT-039	(see above)				
TKT-032	25	DB, R, PB, MC 12 mths	Unclear	Treatment naïve adult and paediatric	Haemoglobin change in 60 U/kg group
Velaglucerase alfa non-randomised studies					
TKT-034	40	OL, MC	High	Adult and paediatric treatment experienced with imiglucerase	Safety
TKT-025/ext.	12 / 9	OL, Phase 1/2	High	Adults w/ intact	Haemoglobin,

Trial	N	Design/duration	Risk of bias	Patient population	Primary outcomes (Change from baseline)
		+ext 9 mths + 5 yrs		spleen, treatment naive	platelets, liver /spleen volume, biomarkers
HGT-044	32	OL, ext. of HGT-039 15 mths	High	Adult and paediatric treatment experienced with imiglucerase or velaglucerase	Safety and tolerability

Note: paediatric populations included patients ≥2 and <18 unless otherwise specified
DB=double blind; ext., extension; MC=multi-centre; mths, months; OL=open label; PG, parallel-group; R=randomised
Source: compiled during the evaluation

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

Comparative effectiveness

6.7 Results were updated from the previous submission with new trial data. Key outcomes measured were the same as previously: change from baseline in haemoglobin levels, platelet counts, and spleen and liver volumes. Differences in baseline levels for these measures, and different methods for calculating spleen and liver volumes in the taliglucerase alfa and imiglucerase/velaglucerase studies, limited the comparability of these results.

Main outcomes: Mean (SD) change from baseline to 9/12 months in the key studies

Treatment arm	Change at 9/12 months, Mean (SD)			
	Spleen volume (%)	Hb concentration (g/dL)	Liver volume (%)	Platelet count (/mm^3)
PB-06-001 (9 months)				
Taliglucerase 30U/kg (N=15)	-26.9% (7.8)	+1.6 (1.4)	-10.5% (11.3)	+11,427 (20,214)
Taliglucerase 60U/kg (N=16)	-38.0% (9.4)	+2.2 (1.4)	-11.1% (6.7)	+41,494 (47,063)
Grabowski 1995 (9 months)				
Imiglucerase 60U/kg (N=15)	-47.1% (13.7)[a]	+2.5 (RNG +0.4, +5.8)	-21.4% (10.8)[a]	*+30,867 (20,594)*
Alglucerase* 60U/kg (N=15)	-42.2% (6.9)[a]	+2.3 (RNG +0.5, +4.3)	-16.4% (8.4)[a]	*+25,067 (21,059)*
HGT-039 (9 months)				
Imiglucerase 60U/kg (N=17)	NR [b,c]	+1.5 (SE 0.3)	NR [c]	*+147,433 (97,506)*
Velaglucerase 60U/kg (N=17)	NR [b,c]	+1.6 (SE 0.2)	NR [c]	*+101,063 (61,268)*
TKT-032 (12 months)				
Velaglucerase 45U/kg (N=13)	-39.9% [c] (NR)	+2.4 (SE 0.5)	-6.2% [c] (NR)	+40,920 (NR)
Velaglucerase 60U/kg (N=12)	-50.4% [c] (NR)	+2.4 (SE 0.3)	-17.0% [c] (NR)	+50,880 (NR)

Source: Section B.6 of the resubmission; Velaglucerase EMA report; Grabowski 1995
Abbreviations: Hb, haemoglobin; RNG, range; SD, standard deviation; SE, standard error
Numbers in italics were calculated during the evaluation. Platelet counts were converted from 10^9/L to mm^3 where applicable, and some rounding errors may have occurred as a result.
[a] The number of patients with 9 month results is unclear

[b] N=7 in each arm due to exclusion of 10 splenectomised patients per arm.
[c] Spleen and liver volumes for studies HGT-039 and TKT-032 were reported as change from baseline in normalised organ volumes, and cannot be directly compared to results for the other key trials.
* Alglucerase is an alternative enzyme replacement therapy that was assessed alongside imiglucerase in the Grabowski et al (1995) study. Imiglucerase has completely replaced the use of alglucerase in Australian clinical practice.

6.8 Responder analyses were presented in the resubmission at the 9 month time point for patients taking 60 U/kg doses in three of the key trials: PB-06-001, HGT-039 and TKT-032.

Comparative responder analysis results at 9 months

Measure / Response	Trial PB-06-001	Trial HGT-039		Trial TKT-032
	Taliglucerase alfa 60U/kg (N=16)	Imiglucerase 60U/kg (N=17)	Velaglucerase alfa 60U/kg (N=17)	Velaglucerase alfa 60U/kg (N=12)
Haemoglobin				
Good	87.5%	41.2%	52.9%	58.3%
Moderate	12.5%	41.2%	35.3%	41.7%
No	0%	17.6%	11.8%	0%
Platelets				
Good	56.3%	100%	87.5%	50.0%
Moderate	6.3%	0%	12.5%	8.3%
No	37.5%	0%	0%	41.7%
Liver				
Good	0%	NR		NR
Moderate	83.3%			
No	16.7%			
Spleen				
Good	85.7%	100%	100%	NR
Moderate	14.3%	0%	0%	
No	0%	0%	0%	

Note: Definitions of Good, Moderate and No response are presented in Table B.5.3 of the commentary
Abbreviations: NR, not reported.
Source: Table 189, pB.273 of the resubmission

6.9 The source of these data was not specified in the resubmission, and for Trial PB-06-001 and TKT-032 could not be found or verified during the evaluation. The ESC noted the sources had been provided in appendix 1 of the pre-sub-committee response (PSCR) (p5-6).

6.10 The responder analysis indicated that between 62.6% and 100% of taliglucerase alfa treated patients achieved a good or moderate response across all 4 endpoints. The resubmission claimed that these results are comparable to response rates for imiglucerase and velaglucerase. Given that there were differences in proportions of good and moderate responders, limitations with the trial designs and low patient numbers, the ESC advised that it is difficult to determine whether taliglucerase alfa is non-inferior to imiglucerase and velaglucerase based on the evidence presented.

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

Comparative harms

6.11 Similar adverse event rates were reported for the 30 U/kg and 60 U/kg taliglucerase alfa treatment arms of the PB-06-001 trial. Across all the taliglucerase alfa studies the most frequently reported treatment related adverse events (>2%) were headache (6.9%), infusion related reaction (6.0%), pruritus (6.0%), hypersensitivity (4.3%), nausea (3.4%), abdominal pain (2.6%), weight increased (2.6%), rhinorrhoea (2.6%), sneezing (2.6%), erythema (2.6%) and flushing (2.6%). Treatment related adverse events in the paediatric patients were gastrointestinal inflammation (6.3%), vomiting (6.3%), chest discomfort (6.3%), pain in extremity (6.3%), throat irritation (6.3%). One paediatric subject experienced a severe treatment-related gastrointestinal inflammation, which led to hospitalisation.

6.12 The resubmission presented immunogenicity data for 71 taliglucerase alfa patients from the included trials. Anti-taliglucerase alfa antibodies were detected in 24 (34%) patients. The resubmission noted an association between anti-taliglucerase alfa antibodies and type 1 hypersensitivity events. For comparison, no velaglucerase patients (n=17) and four imiglucerase patients (n=17; 24%) developed anti-drug antibodies in the HGT-039 trial. In Grabowski (1995), 3 of 15 patients (20%) developed antibodies.

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

Benefits/harms

6.13 Comparative benefits data for taliglucerase alfa versus imiglucerase and velaglucerase alfa were limited to a naïve comparison of responder rates. The evaluation observed that there was insufficient data to assess comparative harms.

6.14 A summary of the comparative benefits is presented in the table below.

Summary of comparative benefits and harms for 60 U/kg dose in key trials

Measure	Trial PB-06-001	Trial HGT-039		Trial TKT-032
	Taliglucerase, n/N (events/ 100 patients)	Imiglucerase, n/N (events/ 100 patients)	Velaglucerase, n/N (events/ 100 patients)	Velaglucerase, n/N (events/ 100 patients)
Benefits – Good or Moderate Response				
Haemoglobin: Increase of > 0.5 g/dL	16/16 (100)	14/17 (82)	15/17 (88)	12/12 (100) [c]
Platelets: Increase of > 15x10 ^{9}/L	10/16 (63)	7/7 (100) [a]	8/8 (100) [a]	7/12 (58) [c]
Liver: Reduction of ≥10% volume	13/16 (81)	NR	NR	NR
Spleen: Reduction of ≥10% volume	16/16 (100)	6/6 (100) [b]	7/7 (100) [b]	NR
Harms – adverse events reported in clinical trials				
There are insufficient data to assess comparative safety				

Abbreviations: NR, not reported
Note: The resubmission presented percentages only for Response categories for all outcomes. Raw numbers have been estimated in the evaluation.
Note: Definitions of Good, Moderate and No response are presented in Table B.5.3 of the commentary
[a] Only patients with platelet counts below normal at baseline were included
[b] Excludes splenectomised patients
[c] The source for these responder rates could not be found during the evaluation, and the data could not be verified. Rates per 100 patients are estimated based on the total number of patients in the velaglucerase 60U/kg arm.
Source: compiled during the evaluation

6.15 On the basis of evidence presented by the resubmission, for every 100 patients treated with taliglucerase alfa :

- All 100 patients would have a good or moderate improvement in haemoglobin levels;
- 63 patients would have a good or moderate improvement in platelet counts;
- 81 patients would have a good or moderate improvement in liver volume; and
- All 100 patients would have a good or moderate improvement in spleen volume.

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

Clinical claim

6.16 The resubmission claimed that taliglucerase alfa achieves similar treatment efficacy outcomes to velaglucerase alfa and imiglucerase, and has a non-inferior safety and tolerability profile. The previous March 2012 submission made a similar claim regarding efficacy but made no claims regarding safety.

6.17 Based on the evidence provided in the resubmission, the ESC advised that there is a trend in the results that was suggestive of non-inferiority in efficacy and safety but that the resubmission's claim was not robustly supported by the evidence presented.

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

Economic analysis

6.18 The resubmission presented a cost-minimisation analysis.

6.19 The evaluation questioned whether it was appropriate for taliglucerase alfa to be cost-minimised against products that have previously been considered non-cost-effective by the PBAC (Velaglucerase alfa Public Summary Document, November 2011/addendum March 2012).

6.20 The ESC advised that a cost-minimisation approach was in line with PBAC Guidelines on choice of comparator (i.e. the therapy most likely to be replaced) and the type of clinical claim made (i.e. non-inferiority).

6.21 The resubmission assumed a 1:1:1 dose equivalence between taliglucerase alfa, imiglucerase and velaglucerase alfa based on the clinical trials and the recommended doses in the Product Information (PI).

6.22 Dosing information was not consistent across the Product Information (PI) documents for the three therapies in regards to statements about switching therapies (e.g.

taliglucerase alfa's PI suggests starting at the same dose that a patient was previously treated with imiglucerase but does not mention velaglucerase patients switched to taliglucerase alfa; velaglucerase's PI simply states 'other enzyme replacement therapy', imiglucerase's PI remains silent on patients switched from taliglucerase alfa or velaglucerase). The evaluation noted that there is very limited evidence to support the equivalence of taliglucerase alfa vs imiglucerase/velaglucerase at lower doses, particularly in treatment naïve patients.

6.23 The ESC advised that while the evidence showing that patients switched from alternative enzyme replacement achieve the same results when treated with taliglucerase alfa is not conclusive, a 1:1:1 ratio probably appeared reasonable given that all three therapies have been studied within the same range of 15 – 60 U/kg fortnightly. The ESC further noted that the PBAC has previously considered that velaglucerase and imiglucerase appear clinically equi-effective at a 1:1 dose ratio (November 2011 velaglucerase alfa Public Summary Document).

6.24 The cost-minimisation analysis was based on drug costs only. The resubmission assumed the ex-manufacturer cost of imiglucerase and velaglucerase was [redacted] per 200 U vial.

6.25 The submission proposed volume-based pricing for taliglucerase alfa, with an ex-manufacturer cost of [redacted] per 200 U vial for the first ten patients (patients currently receiving taliglucerase alfa through a special access scheme), and [redacted] per 200 U vial per additional patient. This price was lower than that proposed in the 2012 submission.

6.26 The resubmission assumed that there is no difference in administration costs between treatments as all therapies are administered by intravenous infusion once every two weeks. The evaluation noted that whilst this may be reasonable at face value, the impact of home infusion programs for taliglucerase alfa and velaglucerase was unclear. The ESC noted that the PSCR (p4) stated that in-home infusion services would be provided by the sponsor and would not be at a cost to Government.

6.27 The resubmission assumed that there are no differences in the costs of managing adverse events between treatments as all treatments have comparable safety profiles. The evaluation noted that this assumption may not be reasonable given that there were insufficient data reported in the included studies to compare the safety profiles of taliglucerase alfa with other enzyme replacement therapies. However, it was noted by the evaluation that the costs of treating these adverse events are likely to be minimal relative to the actual drug treatment costs.

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

Taliglucerase alfa cost/patient/year: [redacted]

6.28 The cost/patient/year for taliglucerase alfa was calculated based on fortnightly infusions (26 infusions/year) with an average dose of 30.86 U/kg (from Szer 2014 – Australian sample) and average body weight of 68 kg (from Trial PB-06-001). Actual costs per patient would vary as dosage is individualised to each patient. Treatment is

ongoing. The ESC noted international literature[1,2] indicating lower starting doses (15 U/kg every two weeks in adults and 30 U/kg every 2 weeks in children) can be used and appear equally effective. This, along with the likely higher average body weight of 75 kg, would impact cost.

Estimated PBS usage & financial implications

6.29 This resubmission was not considered by DUSC.

6.30 A mixed market-share and epidemiological approach was taken. The ESC noted that the PSCR (p3) explained that the number treated with taliglucerase alfa was based on the number of current Special Access Scheme patients on taliglucerase alfa, a proportion (20%) of the current imiglucerase and velaglucerase patients switching to taliglucerase alfa and a single incident patient. An incidence of Gaucher disease of 4.35 patients per year was estimated from Meikle et al. (1999). If Type 2 or 3 Gaucher disease is taken into account, this could equate to less than one patient per year being eligible for treatment with taliglucerase alfa as the proposed listing limits treatment to Type 1 Gaucher disease. The submission assumed that no more than 1 out of the 4 newly diagnosed Gaucher disease patients per year would be treated with taliglucerase alfa, but acknowledged that there is no evidence to support this number. The resubmissions estimates of use and financial implications are shown below.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	20	21	22	23	24
Number treated – March 2012	14	15	16	17	18
Uptake rate	20.71%	20.71%	20.71%	20.71%	20.71%
Uptake rate – March 2012	20%	20%	20%	20%	20%
Vials dispensed	6160	6475	6791	7107	7422
Vials dispensed – March 2012	6728	7166	7166	7751	8336
Estimated net cost to PBS (ex-manufacturer)					
Net cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS March 2012	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to Government					
Net cost to Gov't	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Gov't March 2012	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Compiled during the evaluation

Note: Estimates of vials dispensed are lower in the current resubmission due to a lower average dose (30.86U/kg vs mix of 34.3% at 30U/kg and 65.7% 60U/kg) and body weight (68kg vs 75kg) used compared to the March 2012 submission

6.31 The PSCR (p4) acknowledged that the weighted average price used in Section E of the resubmission was incorrect and should have been [redacted] as in Section D of the resubmission.

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

[1] Zimran, A. How I treat Gaucher Disease. August 2011; Blood:118(6).

[2] Tukan et al. Achievement of Therapeutic Goals with Low-Dose Imiglucerase in Gaucher Disease: A single-centre experience. 2013: Advances in Haematology.

Quality Use of Medicines

6.32 The resubmission proposed the development and provision of educational material to patients and health professionals; provision of an in-home infusion service to patients whose infusions are well-tolerated (performed under the direction of treating clinicians), the implementation of a risk management plan for post-marketing product surveillance, and the entry of Australian taliglucerase alfa-treated patients into the international taliglucerase alfa registry.

6.33 The ESC considered it preferable to have more than one enzyme replacement therapy for Gaucher disease available for Australian patients to manage potential cases of hypersensitivity or stock shortages with any individual product.

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

7 PBAC Outcome

7.1 The PBAC rejected the submission to list taliglucerase alfa on the PBS on the basis that equivalent comparative efficacy and safety to imiglucerase and velaglucerase alfa were not established. Although the PBAC accepted that taliglucerase alfa provides a clinical benefit to patients, the clinical claim that taliglucerase alfa provides equivalent health outcomes to imiglucerase and velaglucerase alfa was not accepted as the comparability of the results between the trials was limited. Therefore the cost-minimisation analysis was not accepted.

7.2 The PBAC recognised that imiglucerase and velaglucerase alfa are not listed on the PBS and have not been considered to be cost-effective for listing on the PBS but agreed that these two treatments were the appropriate comparators for the reasons outlined by the ESC. As velaglucerase alfa was now considered to be an appropriate additional comparator, it was noted that the resubmission presented clinical evidence reflecting this.

7.3 The PBAC noted that the clinical evidence presented in the resubmission continued to lack head-to-head direct randomised trial control data but that the resubmission had presented all previous studies with updated data were available, plus one new non-randomised Australian study, and five randomised and non-randomised velaglucerase alfa studies.

7.4 The PBAC observed that the comparative efficacy results suggested that all treatments are associated with improvements in key outcomes. Similar results were seen with taliglucerase alfa for both children and adults, after switching from imiglucerase, and improvements were maintained over the longer term. However, the PBAC agreed with the ESC advice that differences in baseline values, outcome measurements and methods of measurement of organ volume limited the comparability of results between the trials and made it difficult to determine with an adequate level of certainty whether taliglucerase alfa is non-inferior to imiglucerase and velaglucerase alfa.

7.5 In terms of comparative safety, the PBAC, noted that adverse events reported in the imiglucerase and velaglucerase studies were similar to those in the taliglucerase alfa

studies. However, as there were insufficient data available to allow for a formal comparison of safety profiles of taliglucerase alfa, imiglucerase and velaglucerase alfa, the PBAC could not be sufficiently certain that taliglucerase alfa has a non-inferior safety profile compared to the other two treatments.

7.6 Therefore, the resubmission's clinical claim that taliglucerase alfa achieves similar treatment efficacy outcomes to velaglucerase alfa and imiglucerase and has a non-inferior safety and tolerability profile was not accepted by the PBAC. This had implications for the economic analysis.

7.7 The PBAC considered a cost-minimisation analysis to be an appropriate approach to the economic comparison based on the resubmission's clinical claim of non-inferiority. However, as noted above, the PBAC did not accept the submission's clinical claim of non-inferiority and therefore the basis for a cost-minimisation analysis was inadequate. Given that the PBAC had previously considered the comparators not adequately cost-effective to allow listing on the PBS, the PBAC considered that taliglucerase alfa would also not be adequately cost-effective to recommend listing on the PBS based on the evidence presented thus far.

7.8 With respect to the resubmission's estimated PBS usage and financial implications, the PBAC noted the ESC's concerns regarding the change in body weight used in the current submission compared to the March 2012 submission. ESC had considered that an average patient weight of 75 kg (as opposed to 68 kg) is more reasonable and supported by trial evidence (trial PB-06-004 had an average patient weight of 74.9 kg), and considered that as a result, the number of vials dispensed was likely to have been an underestimated. The PBAC considered that an analysis of existing Australian patients currently on imiglucerase and velaglucerase alfa would aid in determining the likely weight of taliglucerase alfa patients. The PBAC further noted that despite the price offered in the resubmission being lower than in the previous submission, there were smaller cost savings to Government estimated in the resubmission than in the 2012 submission. This was due to an increased estimate in patient numbers and number of vials dispensed. The PBAC considered this increase in the estimate to reflect the uncertainty associated with defining the eligible patient population.

7.9 The PBAC considered that in any future resubmission to list taliglucerase alfa on the PBS, the evidence would need to provide further certainty that taliglucerase alfa provides equivalent benefits compared to imiglucerase and velaglucerase alfa and for provide a formal comparison of comparative safety. Although briefly addressed in the pre-PBAC response, the PBAC considered that any resubmission should also address any evidence suggesting that taliglucerase alfa could be used at a lower dose than that proposed in the submission yet still provide an equivalent treatment effect especially noting the high proposed price per mg of drug. Finally, the PBAC considered that an analysis of existing Australian patients currently on imiglucerase and velaglucerase alfa may also aid in determining the likely weight of taliglucerase alfa patients and the financial implications for Government of subsidising taliglucerase alfa.

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

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

Pfizer Australia looks forward to working with the LSDP to obtain listing of Elelyso for the treatment of Australian patients with Gaucher Disease