5.10 PEGUNIGALSIDASE ALFA, Solution for I.V. injection, 20 mg in 10 mL vial, Elfabrio®, Chiesi Australia Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for the treatment of Fabry disease (FD).

1.2 The submission stated that listing was requested on the basis of a cost-minimisation approach versus migalastat, with a request for a price premium of % over the estimated annual cost of migalastat. The submission did not present a cost-minimisation approach to the proposed main comparators (agalsidase alfa and agalsidase beta), claiming that both medications are currently listed on the Life Saving Drugs Program (LSDP) and have not demonstrated cost-effectiveness in past consideration by the Pharmaceutical Benefits Advisory Committee (PBAC). This was appropriate.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults with confirmed Fabry disease
Intervention	Pegunigalsidase alfa
Comparator	Clinical comparator • Current enzyme replacement therapy (ERT), agalsidase alfa and agalsidase beta Secondary comparator • Migalastat
Outcomes	Efficacy • Mean annualised change in $eGFR_{CKD-EPI}$ • LVMI (g/m^2) preferably by MRI (echocardiogram can be used as an alternative) • Plasma lyso-Gb3 • Plasma Gb3 • Urine lyso-Gb3 • UPCR (spot urine test) • Frequency of pain medication use • Exercise tolerance (stress test) Safety • Frequency, severity, and duration of TEAEs • Clinically significant laboratory abnormalities • ECG changes from baseline • Physical examination findings • Injection site reactions following study drug administration • Anti-pegunigalsidase alfa antibodies Humanistic • EuroQol 5 Dimension 5 Level (EQ-5D-5L), a generic questionnaire for measuring quality of life in the categories of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. • Mainz Severity Score Index (MSSI) provides scores for general, neurological, cardiovascular, kidney, and overall assessments of symptom severity. • Short Form Brief Pain Inventory (BPI) questionnaire.
Clinical claim	Pegunigalsidase alfa is non-inferior to agalsidase alfa and agalsidase beta providing an alternative option for both ERT-naïve and ERT-experienced patients with an improved tolerability profile and reduced immunogenicity compared to agalsidase beta while maintaining the renal and cardiac functions.

Source: Table 1.1-2, p6 of the submission.
Abbreviations: ECG, electrocardiograph; eGFR, estimated Glomerular Filtration Rate; $eGFR_{CKD-EPI}$, estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation; Gb3, globotriaosylsphingosine; LVMI, Left Ventricular Mass Index; MRI, magnetic resonance imaging; TEAE, treatment emergent adverse event; UPCR, Urine Protein/Creatinine Ratio.

1.3 The proposed population presented in the PICO is broader than the proposed Pharmaceutical Benefits Scheme (PBS) population described in the submission. It is also broader than the eligible population accessing FD treatments on the LSDP which is restricted to patients presenting with end-organ damage.

2 Background

Registration status

2.1 Pegunigalsidase alfa was Therapeutic Goods Administration (TGA) registered on 26 May 2025 for "long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease" (Product Information (PI)). The clinical

indication in the PI is broader than the population proposed in the submission, which is restricted to FD patients with end-organ damage.

Previous PBAC consideration

2.2 This is the first consideration of pegunigalsidase alfa by the PBAC.

2.3 Medicines for the treatment of FD have been included under the LSDP since 2004, with the listing of ERTs, agalsidase alfa and agalsidase beta. Migalastat was listed on the LSDP for treatment of FD in 2018.

2.4 The PBAC has previously considered migalastat in March 2017, July 2017, November 2017, December 2022, March 2024 and May 2024. Subsequent to the November 2017 consideration, migalastat was included on the LSDP.

2.5 In December 2022, the PBAC recommended the PBS listing of migalastat for the treatment of FD in patients 16 years of age and older who have an amenable mutation in response to a referral from the LSDP Expert Panel (EP). The PBAC considered that the cost-effectiveness of migalastat would be acceptable if the cost per patient per year was no higher than the cost of ERT for a patient weighing 45 kg (paragraph 5.1, migalastat, Public Summary Document [PSD], December 2022 PBAC meeting).

2.6 In March 2024, a request was made to the PBAC to reconsider migalastat's listing and to amend restriction criteria to be consistent with international clinical guidelines for FD. The PBAC recommended the listing of migalastat for the treatment of FD in patients aged 12 years of age and older who have an amenable mutation and evidence of organ involvement/injury (including severe gastrointestinal symptoms, and uncontrolled chronic pain, renal disease, cardiac disease, ischaemic and cerebrovascular disease). The PBAC noted the proposed cost of migalastat was substantially higher than that recommended in December 2022, but considered that, on balance, noting the high clinical need for ongoing access to funded treatments for FD, migalastat was likely to be of high, but acceptable cost effectiveness in the recommended population at the cost per patient per year proposed in the resubmission (paragraph 7.1, migalastat PSD, March 2024 PBAC meeting with May 2024 addendum). The PBAC acknowledged the importance of treating some patients at an earlier stage of disease but considered the clinical effectiveness and cost-effectiveness of this was unknown, and therefore did not recommend extending the listing to patients with classical FD without evidence of organ involvement/injury (paragraph 7.11, migalastat PSD, March 2024 PBAC meeting with May 2024 addendum).

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

3 Requested listing

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

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
PEGUNIGALSIDASE ALFA					
pegunigalsidase alfa 20 mg/10 mL (2 mg/mL) solution in a single-dose vial	Published price Public: [redacted] Private: [redacted]	12	1	5	Elfabrio

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
PEGUNIGALSIDASE ALFA					
pegunigalsidase alfa 20 mg/10 mL injection, 10 mL vial	NEW	1	~~12~~ *1*	5	Elfabrio

Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID		**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) ☒ ~~Section 100 – Highly Specialised Drugs Program - Community Access (Code CA)~~
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required (FULL assessment) in writing via OPA/post/HPOS upload)
		Authority type: ☒ *Complex Authority Required (CAR)*
Prescribing rule level		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.serviceaustralia.gov.au/hpos)* *Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
		Indication: Fabry disease
		Treatment Phase: Initial treatment
		Clinical criteria:
		~~Patient must have at least one of documented deficiency of alpha-galactosidase enzyme activity in blood~~ *Patient must have at least one of: (i) documented deficiency of alpha-galactosidase enzyme activity in blood, (ii) presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity.*

	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity.~~
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2.~~
	AND
	Clinical criteria:
	Patient must be male with Fabry-related renal disease confirmed by at least one of the following: (i) abnormal albuminuria of more than 20 mcg/min, as determined by 2 separate samples at least 24 hours apart, (ii) abnormal proteinuria of more than 150 mg/24 hours, (iii) albumin: creatinine ratio greater than upper limit of normal in 2 separate samples at least 24 hours apart, (iv) renal disease due to long-term accumulation of glycosphingolipids in the kidneys; OR
	Patient must be female with Fabry-related renal disease confirmed by at least one of the following: (i) proteinuria of more than 300 mg/24 hours with clinical evidence of progression, (ii) renal disease due to long-term accumulation of glycosphingolipids in the kidneys; OR
	Patient must have Fabry-related cardiac disease confirmed by at least one of the following: (i) left ventricular hypertrophy, as evidenced by cardiac magnetic resonance imaging (MRI) or echocardiogram data, in the absence of hypertension, (ii) significant life-threatening arrhythmia or conduction defect*, (iii) late gadolinium enhancement or a low T1 on cardiac MRI*; OR
	Patient must have Fabry-related either (i) ischaemic disease, (ii) cerebrovascular disease as shown on objective testing with no other cause or risk factors identified; OR
	Patient must have Fabry-related uncontrolled chronic pain despite the use of recommended doses of appropriate analgesia and antiepileptic medications for peripheral neuropathy; OR
	Patient must have significant Fabry-related gastrointestinal symptoms despite the use of the recommended doses of appropriate pharmacological therapies.
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease.
	Population criteria:
	Patient must be at least 18 years of age.
	Prescribing Instructions: If hypertension is present in patients relying their eligibility on Fabry-related cardiac disease, the prescriber must treat it optimally for at least 6 months prior to submitting the first PBS authority application.
	Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports including the confirmed mutations must be documented in the patient's medical records.
	Prescribing Instructions: The authority application must be made in writing and must include: (1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

	~~**Administrative Advice:**~~ ~~Clinicians should request the number of vials applicable to the patient weight for 1 month of therapy and 1 patient co-payment per month.~~ ***Prescribing Instructions:*** *At the time of authority application, prescribers must request the appropriate number of vials, based on the weight of the patient, to provide sufficient drug for 4 weeks of treatment at the dosage regimen specified in the approved Therapeutic Goods Administration (TGA) Product Information (PI).*
Restriction Summary [new2] / Treatment of Concept: [new2A]	
	Indication: Fabry disease
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated clinical improvement or stabilisation of condition, the details of which must be kept with the patient's record
	AND
	Clinical criteria:
	Patient must not have developed another life threatening/severe disease where long-term prognosis is unlikely to be influenced by ~~pegunigalsidase alfa~~ *this drug*
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease.
Restriction Summary [new3] / Treatment of Concept: [new3A]	
	Indication: Fabry disease
	Treatment Phase: Grandfather arrangement (transition from LSDP-funded Fabry disease therapy)
	Clinical criteria:
	~~Patient must have received prior PBS-subsidised treatment with this drug for this condition~~ *Patient must have previously received treatment with enzyme replacement therapy for this condition funded under the Australian Government's Life Saving Drugs Program (LSDP) prior to [PBS listing date].*
	AND
	Clinical criteria:
	Patient must have demonstrated clinical improvement or stabilisation of condition, the details of which must be kept with the patient's record
	AND
	Clinical criteria:
	Patient must not have developed another life threatening/severe disease where long-term prognosis is unlikely to be influenced by ~~pegunigalsidase alfa~~ *this drug*
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.

	Population criteria:
	Patient must be at least 18 years of age.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease
	Prescribing Instructions: *A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.*
	Prescribing Instructions: *Confirmation of eligibility for treatment with diagnostic reports including the confirmed mutations must be documented in the patient's medical records.*
FULL	***Prescribing Instructions:*** *The authority application must be made in writing and must include:* *(1) details of the proposed prescription; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*

3.2 The submission proposed a published approved ex-manufacturer price (AEMP) of $ per 20 mg vial, based on a % premium on the annual cost of migalastat (see paragraph 6.63). The submission requested a Special Pricing Arrangement (SPA) for pegunigalsidase alfa but did not propose an effective price as the effective price for migalastat is not known. The rationale provided for the price premium is not well justified given the evidence presented (see paragraph 6.58).

3.3 The Fabry disease therapy migalastat is listed on the PBS as General Schedule (Authority Required (written)) for initial treatment and Grandfather arrangement listings, and Authority Required (telephone/electronic) for continuing treatment.

3.4 The submission stated that as part of its requested S100 listing, it is seeking public/private hospital and community access. If pegunigalsidase alfa is listed under S100 HSD as a Complex Authority Required (CAR) (written) listing, this would allow dispensing in public/private hospitals and community pharmacies.

3.5 The submission requested medical practitioners as the sole prescriber type for this listing, consistent with the migalastat listing. As such, a treatment criterion stating that patients 'must be treated by a physician with expertise in the management of Fabry disease' was requested.

3.6 The submission included the Population Criterion 'Patient must be at least 18 years of age' in the requested listing. The PI states that the safety and efficacy of pegunigalsidase alfa has not been established in children and adolescents aged 0-17 years (or in patients older than 65 years).

3.7 The submission requested a maximum quantity of 1 pack of 12 x 20 mg/10 mL single-dose vials with 5 repeats. The recommended dose for pegunigalsidase alfa in the PI is 1 mg/kg of body weight every 2 weeks. The submission stated that the requested maximum quantity was based on a person with body weight of 120 kg (i.e., requiring 120 mg dose (6 single-dose vials) fortnightly, or 12 single-dose vials per month). The submission also stated that in the BALANCE trial the average weight of participants

was 78.9 kg (i.e., requiring 4 single-dose vials fortnightly, or 8 single-dose vials per month). Dose adjustments were also conducted in the BALANCE trial when a patient's body weight changed by at least 25% from baseline at months 6, 12 or 18. The PI also states that pegunigalsidase alfa comes in packs sizes of 1, 5 or 10 vials per carton (i.e., there is no pack of 12 vials).

3.8 Considering that pegunigalsidase alfa is administered at a variable dose (i.e., a weight-based dosing regimen), amending the maximum quantity to 1 and including a Prescriber Instruction that instructs prescribers to request the appropriate quantity sufficient for 4 weeks based on the patient's weight was suggested (as shown in the proposed listing).

3.9 The submission stated that pegunigalsidase alfa is not interchangeable with other PBS-listed or LSDP-listed medicines. This appears to contradict the rationale provided to justify the nomination of the LSDP listed medicines, agalsidase alfa and agalsidase beta, as comparators (see paragraph 5.1). ERTs have a similar pharmacological action.

3.10 The proposed PBS restrictions for pegunigalsidase alfa are broadly in line with the patient eligibility criteria detailed in the LSDP treatment guideline for FD.[1] Three of the clinical criteria included in the proposed PBS restriction for initiating treatment are not included in the eligibility requirements of the LSDP guideline but are consistent with the migalastat PBS restriction:

- Patient must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m² (the PI for pegunigalsidase alfa states that no dose adjustment is needed in patients with renal or hepatic impairment).
- Patient must have Fabry-related cerebrovascular disease as shown on objective testing with no other cause or risk factors identified.
- Patient must have significant Fabry-related gastrointestinal symptoms despite the use of the recommended doses of appropriate pharmacological therapies.
- Patient must have Fabry-related cardiac disease confirmed by at least one of the following: (i) left ventricular hypertrophy, as evidenced by cardiac magnetic resonance imaging (MRI) or echocardiogram data, in the absence of hypertension, (ii) significant life-threatening arrhythmia or conduction defect'. The current PBS listing for migalastat includes also include the third option '(iii) late gadolinium enhancement or a low T1 on cardiac MRI'.

3.11 The requested restrictions are narrower than the indication in the TGA-approved PI, which does not restrict to patients with end-organ damage. The targeted patient population is not consistent with the patient population of the BALANCE trial which (i) did not restrict eligibility to patients with end-organ damage as is proposed for pegunigalsidase alfa, and (ii) included treatment experienced patients (see

[1]Department of Health and Aged Care. Life Saving Drugs Program Fabry Disease Guidelines. Available at www.health.gov.au/resources/publications/life-saving-drugs-program-fabry-disease-guidelines?language=en

paragraph 6.10). The submission stated that the sponsor does not propose to extend the listing to patients with classical FD without evidence of end organ involvement/injury.

3.12 The submission also requested a PBS restriction for Grandfathered patients who are electing treatment with pegunigalsidase alfa and are currently on or transitioned to a different drug through the LSDP. These patients are required to remain on the same drug for a period of at least 12 months, unless there is objective clinical evidence of ongoing clinical deterioration or significant adverse reactions (submission). The requested Grandfather restriction did not stipulate the 12-month criterion. Given the claim of non-inferiority and that there is no evidence to support a clinical advantage of treatment with pegunigalsidase alfa over other ERTs, it is unclear how many patients would be electing to switch over from ERTs, with the switch being based on patient and/or clinician preference. The Secretariat has suggested the inclusion of a Population Criterion and Prescriber Instruction that limits access to the GF treatment phase to once only, in line with the GF listing on the PBS for migalastat.

3.13 In its March 2024 consideration of migalastat, the PBAC noted the grandfathering restriction may need to be retained for longer than the standard timeframe of 12 months, depending on the transition of other treatments for FD to the PBS (paragraph 7.4 migalastat public summary document, May 2024 PBAC meeting).

3.14 The submission requested the following clinical criterion in the GF restriction: 'Patient must have demonstrated clinical improvement or stabilisation of condition, the details of which must be kept with the patient's record'. This criterion is not included in the GF restriction for migalastat. The intent of the pegunigalsidase alfa GF restriction is to allow patients who are using LSDP funded ERT therapies (i.e., agalsidase alfa and agalsidase beta) to access pegunigalsidase alfa through the PBS.

3.15 The submission did not propose any flow-on changes to PBS-listed medicines. The following changes to the migalastat PBS-listing and requested listing for pegunigalsidase alfa were proposed:

- Addition of the clinical criterion 'the treatment must be the sole PBS subsidised therapy for this condition' (to prevent concomitant use of FD therapies).
- Addition of a new treatment phase with specific criteria that allows switching from pegunigalsidase alfa to migalastat and vice versa.

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

4 Population and disease

4.1 FD is a progressive, X-linked lysosomal storage disorder caused by a deficiency of the lysosomal enzyme α-galactosidase A (α-GAL A), due to a mutation in the galactosidase alpha (α-GAL) gene. This deficiency leads to progressive accumulation of glycolipids (mainly globotriaosylceramide [Gb3] and globotriaosylsphingosine [lyso-Gb3]) in the plasma and lysosomes of cells[2,3,4,5], disrupting metabolic processes and inducing cell death, ultimately resulting in progressive vital organ dysfunction and a reduced life expectancy.

4.2 The clinical manifestations of FD are diverse, encompassing renal dysfunction, cardiovascular issues, neuropathic pain, cerebrovascular disease, gastrointestinal issues, angiokeratomas and hypohidrosis.[3,4,5,6] Given the multisystemic nature of the disease, symptoms can be diverse and vary in severity with a number of symptoms, such as neuropathic pain and gastrointestinal issues, significantly impacting patients' quality of life (QoL).[6,7,8,9,10]

4.3 The severity of FD is dependent on the extent of α-GAL A deficiency, with FD classified into two subtypes defined by α-GAL A enzyme levels – classic FD and late onset FD. Classic FD is characterised by complete (or near-complete) absence of α-GAL A enzyme levels and early multisystem involvement, with patients typically presenting with early-onset pain and rash. Late onset FD is associated with residual α-GAL A activity and exhibits slower progression, delayed symptom onset and more limited organ involvement.[11] Approximately 30% of FD patients in Australia present with

[2] Biegstraaten et al., (2015), 'Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document', Orphanet J Rare Dis, 10.
[3] Laney et al., (2013), 'Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors', J Genet Couns, 22, 5.
[4] Ortiz et al., (2018), 'Fabry disease revisited: Management and treatment recommendations for adult patients', Mol Genet Metab, 123, 4.
[5] Wanner et al., (2018), 'European expert consensus statement on therapeutic goals in Fabry disease', Mol Genet Metab, 124, 3.
[6] Nicholls et al., (2024), 'Fabry-specific treatment in Australia: time to align eligibility criteria with international best practices', Intern Med J, 54, 6.
[7] Arends et al., (2015), 'Quality of life in patients with Fabry disease: a systematic review of the literature', Orphanet Journal of Rare Diseases, 10, 1, https://doi.org/10.1186/s13023-015-0296-8.
[8] Arends et al., (2018), 'Phenotype, disease severity and pain are major determinants of quality of life in Fabry disease: results from a large multicenter cohort study', J Inherit Metab Dis, 41, 1.
[9] MacDermot et al., (2001), 'Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females', J Med Genet, 38, 11.
[10] MacDermot et al., (2001), 'Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males', J Med Genet, 38, 11.
[11] National Organization for Rare Disorders, (2019), Fabry Disease, available at https://rarediseases.org/rare-diseases/fabry-disease/

symptoms of end-organ damage, with the majority (approximately 85%) of these eligible patients accessing treatment through the LSDP.[12]

4.4 In the absence of a cure, treatment of FD is centred around symptom management and halting disease progression.[13] ERTs (agalsidase alfa and agalsidase beta) and oral chaperone therapies (OCTs) (migalastat) are currently available treatments in Australia, with migalastat indicated for FD patients with an amenable mutation.

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

5 Comparator

5.1 The submission nominated agalsidase alfa and agalsidase beta as the main comparators as they are (i) of the same pharmacological class, which the submission claimed pegunigalsidase alfa would be a direct replacement to, and (ii) are the only ERT treatments currently available for patients with FD (with or without amendable mutation). The choice of comparators was appropriate, however migalastat should also be considered an equally relevant comparator (paragraph 5.3).

5.2 Agalsidase alfa and agalsidase beta are indicated as ERTs for the treatment of FD in paediatric (≥6.5 years old for agalsidase alfa) and adult patients and have been listed on the LSDP since 2004. The treatments target and catalyse the accumulation of Gb3 to improve or stabilise renal function, reduce pain, improve pain-related QoL, and improve cardiac function.[14,15]

5.3 The submission also nominated migalastat as a secondary comparator for patients with an amenable mutation as it is likely to be offered as first choice of treatment given that it can be taken orally (compared to intravenous [IV] infusions for ERTs). Migalastat is equally a relevant comparator given its place in therapy alongside other ERTs (as indicated by the proposed treatment algorithm).

5.4 The Pre-Sub-Committee Response (PSCR) stated that migalastat is an additional comparator for ERTs in patients with an amenable mutation and is anticipated to have the predominant market share for this sub-group population. The PSCR claimed that patient and clinical preference might support the use of ERT for some patients. The PSCR further stated that pegunigalsidase alfa, if listed on the PBS, would be an alternative to ERTs currently on the LSDP. The PSCR stated that pegunigalsidase alfa is

[12] Australian Government, (2023), 'Life Saving Drugs Program (LSDP): Review of Medicines for Fabry disease. Review summary and expert panel recommendations. 2023', Available at www.health.gov.au/sites/default/files/2023-01/life-saving-drugs-program-fabry-disease-review-summary-and-expert-panel-recommendations_0.pdf

[13] Ortiz A., Germain D.P., Desnick R.J., et al., 2018, 'Fabry disease revisited: management and treatment recommendations for adult patients', Mol Genet Metab123(4), pp. 416-27.

[14]https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04048-3&d=20250324172310101&d=20250413172310101

[15]https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2010-PI-04342-3&d=20250321172310101

not expected to increase the overall ERT market but will be a substitute for existing ERTs in patients newly diagnosed with FD who would have otherwise started treatment with agalsidase alfa or agalsidase beta. The PSCR maintained that migalastat should be a secondary comparator.

5.5 The ESC considered that in practice pegunigalsidase alfa is most likely to replace other ERTs (agalsidase alfa and agalsidase beta) which are on the LSDP and considered migalastat is only a comparator for patients with an amenable mutation. The ESC noted that choice of first-line therapy is a clinical decision and individualised for the patient, and all three medicines are clinical comparators for first-line treatment. As migalastat is the only medicine for FD listed on the PBS, the ESC considered it was reasonable to include migalastat as a comparator for the cost-minimisation approach (CMA).

5.6 Migalastat is an OCT that selectively and reversibly binds to the active sites of certain mutant forms of α-GAL A (i.e., amenable mutations) to stabilise and restore α-GAL A activity. It is currently listed on the PBS for treatment of FD in patients aged 12 years of age and older who have an amenable mutation and evidence of organ involvement/injury. Migalastat was initially listed on the LSDP in 2018, before transitioning to the PBS in September 2024.

5.7 There were inconsistencies in the comparators that were used throughout the submission. There was limited clinical evidence presented for the comparison of pegunigalsidase alfa against migalastat. For the cost-minimisation approach, migalastat was used as the comparator and in the financial impact analysis, agalsidase alfa and agalsidase beta were considered as the main treatments that would be replaced. The ESC considered that all three medicines are first-line comparators as they are all used in practice, however as migalastat is the only medicine for FD on the PBS it is the most appropriate comparator for the CMA.

5.8 The pre-PBAC response agreed that migalastat is a relevant comparator, but only for patients with an amenable mutation, and claimed that migalastat was likely to retain a predominant market share in this patient group, although there may be situations where ERTs would be the preferred treatment. The pre-PBAC response maintained that pegunigalsidase alfa would be a direct alternative to other ERTs (agalsidase alfa and agalsidase beta), and that pegunigalsidase alfa would not be expected to grow the market, but act as a substitute to other ERTs for patients newly diagnosed with FD. The pre-PBAC response maintained that ERTs currently on the LSDP should be primary comparators, and migalastat should be a secondary comparator for patients with an amenable mutation and used as a pricing comparator as it is the only medicine for FD listed on the PBS.

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 and welcomed the input from individuals (4), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the challenges with living with FD, including disruption to daily life and reduced ability to participate in physical activity, work, social activities and education due to symptoms, as well as the emotional impact of managing a chronic condition. Input described challenges with using current ERT options, including limited efficacy and suitability, treatment burden and lack of accessibility due to fortnightly administration with agalsidase alfa and restricted eligibility. Benefits of treatment with pegunigalsidase alfa described included its efficacy in stabilising the condition and improving signs and symptoms, fewer disruptions to daily life from treatment administration, improved quality of life, and the provision of another treatment option where current treatments are not viable. Comments also stated that current LSDP criteria prevent access to effective treatment in early stages of disease which could potentially prevent permanent impairment, and broader eligibility criteria would improve access to individuals, particularly for those without the migalastat-amenable mutation. Health professional input stated that pegunigalsidase alfa was well tolerated, however there is a risk of hypersensitivity reactions in some individuals. Health professional input also stated that there are limited treatment options for FD, and current treatment option available are unsuitable in some situations due to risk of infusion complications, eligibility and reduced efficacy.

6.3 The PBAC noted the advice received from Fabry Australia and Fabry Australia Medical Advisory Committee, who were supportive of listing pegunigalsidase alfa on the PBS and the availability of different treatment options so the most appropriate therapy could be used by an individual. Fabry Australia commented that FD has a severe impact on the everyday lives of individuals, and there is currently a gap in treatment access for patients with FD, with some patients ineligible under the LSDP criteria and not having the mutation that is amenable to migalastat.

Clinical studies

6.4 The submission was based on one head-to-head, multicentre, double-blind, Phase III randomised controlled trial (RCT) comparing pegunigalsidase alpha (1 mg/kg every 2 weeks [Q2W]) versus agalsidase beta (1 mg/kg Q2W) over 24 months in symptomatic FD patients with deteriorating renal function who had received agalsidase beta for at least 1 year: BALANCE (N=77). A claim of non-inferiority was made on the outcome of annualised change in eGFR; change from baseline in: Urine

Protein/Creatinine Ratio (UPCR), Left Ventricular Mass Index (LVMI), stress test, plasma lyso-Gb3, plasma Gb3, urine lyso-Gb3, Brief Pain Inventory (BPI) pain severity and Mainz Severity Score Index (MSSI); Fabry clinical events (FCE); change in QoL: EuroQoL-5 Dimension-5 Level (EQ-5D-5L), and adverse events (AEs).

6.5 The submission used the study results of the following five non-comparative studies: BRIDGE, BRIGHT, PB-102-F01, PB-102-F02 and PB-102-F03 as additional evidence to support the clinical claims presented in the BALANCE trial. While these studies were not the primary focus of the evidence base, their results are summarised in paragraphs 6.29, 6.30 and 6.48 for consideration:

- BRIDGE (N=22) was a Phase III, open-label, single arm, switch-over study designed to evaluate the safety and efficacy of 12 months of pegunigalsidase alfa (1 mg/kg Q2W) in adult patients with FD who have been previously treated with agalsidase alfa for ≥2 years.
- BRIGHT (N=30) was a Phase III, open-label, single arm, switch-over study evaluating the efficacy and safety of pegunigalsidase alfa (2 mg/kg every 4 weeks [Q4W]) over a period of 52 weeks in patients with FD who were previously treated with ERT: agalsidase alfa or agalsidase beta, for ≥3 years. The recommended dosing as per the draft PI for pegunigalsidase alfa is 1 mg/kg Q2W.
- PB-102-F01 (N=18) and its extension studies PB-102-F02 (N=16) and PB-102-F03 (N=15) were three Phase I/II, open-label, single-arm studies assessing pegunigalsidase alfa in treatment naive patients or those not receiving treatment in the last six months. Patients were enrolled into one of three dosing groups (0.2 mg/kg, 1.0 mg/kg, 2.0 mg/kg Q2W) and assessed over a three-month period in PB-102-F01, followed by an additional nine-month period in PB-102-F02. PB-102-F03 evaluated 1.0 mg/kg Q2W of pegunigalsidase alfa for up to 60 months with no less than 36 months in patients who successfully completed treatment in studies PB-102-F01 and PB-102-F02.

6.6 The submission also identified two RCTs for migalastat, which have been previously considered by PBAC (paragraph 6.7, migalastat, PSD, March 2024 PBAC meeting):

- ATTRACT (intention to treat [ITT), N=60; modified ITT [mITT] amenable, N=52) was a Phase III, open label, RCT comparing migalastat versus ERT in treatment-experienced FD patients (ERT: agalsidase alfa and agalsidase beta).
- FACETS (ITT, N=67; mITT amenable, N=50) was a Phase III RCT comparing migalastat versus placebo in patients who were ERT treatment-naïve or had not received ERT for six months prior to trial entry.

6.7 There are no head-to-head trials comparing pegunigalsidase alfa and migalastat and the submission did not present an indirect treatment comparison (ITC) to support the clinical claim. The submission instead presented limited evidence on baseline characteristics, data on eGFR and a summary of AEs for ATTRACT, and brief results for FACETS, to support the clinical claim against migalastat. Given that migalastat is also

a relevant comparator (among FD patients with amenable disease) and it was used as the comparator in the cost-minimisation approach, it is important to present the key evidence base for consideration.

6.8 The evidence base for ATTRACT was included across the evaluation as this would be a relevant trial for an ITC comparing pegunigalsidase and migalastat (using ERT as common comparator). FACETS is unlikely to be relevant to the ITC.

6.9 Details of the studies presented in the submission to support the claim are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
BALANCE NCT02795676	A Randomized, Double-blind, Active Control Study of the Safety and Efficacy of pegunigalsidase alfa Compared to Agalsidase Beta on Renal Function in Patients with Fabry Disease Previously Treated with Agalsidase Beta (The BALANCE Study).	CSR July 2022
	Wallace et al . Head-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomised phase III BALANCE study.	Journal of medical genetics. 2024 Jun 1;61(6):520-30.
	Lee et al. PCR86 Estimating Health-Related Quality of Life in Fabry Disease for Patients Treated with Enzyme-Replacement Therapy in the BALANCE Randomized Controlled Trial.	Value in Health. 2023 Dec 1;26(12):S465.
	Wallace et al. First results of a head-to-head trial of pegunigalsidase alfa vs. agalsidase beta in Fabry disease: 2-year results of the phase 3 randomized, double-blind, BALANCE study.	Molecular Genetics and Metabolism. 2023 Feb 1;138(2):107351.
BRIDGE NCT03018730	An Open Label Study to Assess the Safety and Efficacy of pegunigalsidase alfa in Patients with Fabry Disease Currently Treated With REPLAGAL® (Agalsidase Alfa).	CSR November 2020
	Linhart et al. Safety and efficacy of pegunigalsidase alfa in patients with Fabry disease who were previously treated with agalsidase alfa: results from BRIDGE, a phase 3 open-label study.	Orphanet Journal of Rare Diseases 2023 Oct 21;18(1):332.
BRIGHT NCT03180840	A Phase 3, Open Label, Switch Over Study to Assess the Safety, Efficacy and Pharmacokinetics of Pegunigalsidase alfa (PEGUNIGALSIDASE ALFA) 2.0 mg/kg Administered by Intravenous Infusion Every 4 Weeks for 52 Weeks in Patients with Fabry Disease Currently Treated With Enzyme Replacement Therapy: Fabrazyme® (Agalsidase Beta) or Replagal™ (Agalsidase Alfa).	CSR November 2021
	Holida et al. A phase III, open-label clinical trial evaluating pegunigalsidase alfa administered every 4 weeks in adults with Fabry disease previously treated with other enzyme replacement therapies.	Journal of inherited metabolic disease. 2025 Jan;48(1):e12795.
	Bernat et al. eP149: Safety and efficacy of pegunigalsidase alfa, every 4 weeks, in Fabry disease: Results from the phase 3, open-label, BRIGHT study.	Genetics in Medicine. 2022 Mar 1;24(3): S91-2.
PB-102-F01 & PB-102-F02 NCT01678898/ NCT01769001	PB-102-F01: A Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of pegunigalsidase alfa Administered by Intravenous Infusion Every 2 Weeks for 12 Weeks to Adult Fabry Patients.	CSR June 2017
	PB-102-F02: An Extension of Phase 1/2, Open Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of pegunigalsidase alfa Administered by Intravenous Infusion Every 2 Weeks for 38 Weeks (9 Months) to Adult Fabry Patients.	CSR June 2017

Trial ID	Protocol title/ Publication title	Publication citation
	Schiffmann et al. Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favourable pharmacodynamics: a 1-year phase 1/2 clinical trial.	Journal of inherited metabolic disease. 2019 May;42(3):534-44.
	Warnock et al. PRX-102 for treating Fabry disease: immunogenicity and PK results from a phase 1-2 study.	Molecular Genetics and Metabolism. 2017;1(120): S137-8.
PB-102-F03 NCT01981720	A Multi Center Extension Study of pegunigalsidase alfa Administered by Intravenous Infusions Every 2 Weeks for up to 60 Months to Adult Fabry Patients.	CSR November 2021
	Hughes D, et al. Long-term safety and efficacy of pegunigalsidase alfa: a multicenter 6-year study in adult patients with Fabry disease.	Genetics in Medicine. 2023 Dec 1;25(12):100968.
ATTRACT NCT01218659	Migalastat for the treatment of Fabry disease. Public Summary Document.	March 2024 PBAC Meeting
	Hughes D, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study.	Journal of Medical Genetics; 2017; 54(4): 288-296.

Source: Table 2.2-1 and Table 2.2-2, pp33-35 of the submission.
Abbreviations: CSR, clinical study report; PBAC, Pharmaceutical Benefits Advisory Committee.
Note: Only the main sources of evidence included in the submission were listed in this table. Conference abstracts presented in the submission were excluded given the availability of full-text publications, from which outcomes were extracted and presented in the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)
BALANCE	77	Phase III, R, DB, MC 24 months	Some concerns[a]	ERT Treatment-experienced FD patients with deteriorating renal function	Primary: annualised change in eGFR (slope) Secondary: change from baseline in: UPCR, LVMI, plasma lyso-Gb3, plasma Gb3, urine lyso-Gb3, BPI pain severity, MSSI, and EQ-5D-5L; FCE and AEs.
BRIDGE	22	Phase III, OL, single arm 12 months	NA[b]	ERT Treatment-experienced FD patients	Annualised change in eGFR (slope); change from baseline in: LVMI, plasma lyso-Gb3, plasma Gb3, urine lyso-Gb3, MSSI, and EQ-5D-5L; FCE and AEs.
BRIGHT	30	Phase III, OL, single arm 52 weeks	NA[b]	ERT Treatment-experienced FD patients	Annualised change in eGFR (slope); change from baseline in: plasma lyso-Gb3, plasma Gb3, urine lyso-Gb3, MSSI, and EQ-5D-5L; and AEs.
PB-102-F01 & PB-102-F02[c]	18	Phase I/II, OL, single arm 12 months	NA[b]	Treatment-naïve FD patients	Annualised change in eGFR (slope); change from baseline in plasma lyso-Gb3 and plasma Gb3.
PB-102-F03	15	Phase I/II, OL, single arm Up to 60 months	NA[b]	Treatment-naïve FD patients	Annualised change in eGFR (slope); change from baseline in plasma lyso-Gb3 and plasma Gb3.
ATTRACT	60 ITT 52 mTT amenable	Phase III, OL, MC, R, 18 months	High	ERT Treatment-experienced FD patients with an amenable mutation	Annualised change in eGFR (slope); change from baseline in LVMI and AEs.

Source: Table 2.2-3, pp38-39 of the submission and Section 2, pp24-106 of the submission.

Abbreviations: AEs, adverse events; BPI, Brief Pain Inventory; DB, double blind; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; ERT, enzyme replacement therapy; FCE, Fabry clinical events; FD, Fabry disease; Gb3, Globotriaosylsphingosine; ITT, intention to treat; MC, multi-centre; LVMI, Left Ventricular Mass Index; mITT, modified intention to treat; MSSI, Mainz Severity Score Index; NA, not assessed; OL, open label; R, randomised; UPCR, Urine Protein/Creatinine Ratio.

[a] There were some concerns regarding attrition bias with more patients discontinuing in the pegunigalsidase alfa arm (5/52=9.6%) compared to the agalsidase beta arm (1/25=4.0%) due to AEs (3.9% vs 0%) and withdrawal of consent (5.8% vs 4.0%), noting the small sample size in each arm (n=52 pegunigalsidase alfa and n=25 agalsidase beta). This leads to an overall risk of bias of some concern.

[b] Risk of bias was not assessed and reported in the submission. It is likely these studies will be with an overall high risk of bias, given the open label nature, single arm and small sample size.

[c] Results of PB-102-F01 & PB-102-F02 were presented together at 12 months. Patients in PB-102-F01 were assessed over three months, followed by an additional nine months in PB-102-F02.

6.11 While the BALANCE trial was assessed with a low risk of selection, performance, detection and reporting bias, there were some concerns regarding attrition bias with more patients discontinuing in the pegunigalsidase alfa arm (5/52=9.6%) compared to agalsidase beta arm (1/25=4.0%) due to AEs (3.9% vs 0%) and withdrawal of consent (5.8% vs 4.0%), noting the small sample size in each arm (n=52 pegunigalsidase alfa and n=25 agalsidase beta). This leads to an overall risk of bias of some concerns.

6.12 The ATTRACT trial was an open label trial assessed with an overall high risk of bias. This is consistent with a prior assessment of migalastat, in which it was determined that due to the small sample size (reduced due to the reclassification of galactosidase alpha gene (GLA) mutations for amenable patients) and variability in the characteristics of the patient population, there was an increased risk of type II errors

(such as would occur if the studies failed to detect an effect for migalastat even where one actually existed) (paragraph 6.6, migalastat, PSD, March 2017 PBAC meeting).

6.13 The key differences between the trial eligibility criteria and proposed PBS listing included:

- The trial allowed patients up to 60 years old, while the proposed listing does not have an upper age limit.
- Patients in the trial required a more specific eGFR range (40-120 mL/min/1.73 m²) with a measurable decline over time (eGFR of ≥2 mL/min/1.73 m²/year), while the proposed listing may include patients with poorer renal function, i.e., requiring a minimum eGFR of 30 mL/min/1.73 m² without considering the slope of decline (based on the migalastat PBS listing).
- Patients in the trial were treatment-experienced (with agalsidase beta) while the proposed listing is for treatment-naïve and treatment-experienced patients (i.e., first- and second-line treatment).

6.14 The treatments arms in the BALANCE trial were balanced across most baseline characteristics. The main differences were*:*

- Agalsidase beta arm had a higher proportion of males (72% vs 55.8%), higher use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) (64% vs 50%), higher proportion of patients with UPCR ≤ 0.5 gram/gram at baseline (80% vs 69.2%), longer duration of previous ERT use (77.3 months vs 65 months) and higher use of premedication for agalsidase beta infusion (60% vs 38.5%) compared to the pegunigalsidase alfa arm. Compared to patients in the pegunigalsidase arm, patients in the agalsidase beta arm had a higher proportion of males (typically have more severe disease manifestations), reported higher use of ACEi or ARBs used to manage cardiovascular conditions, had longer exposure to ERTs and were more heavily premedicated.

6.15 The key differences in the eligibility criteria between BALANCE and ATTRACT trials are as follows*:*

- ATTRACT trial included a broader age range (16-74 years), while BALANCE was restricted to adults between 18 and 60 years.
- ATTRACT trial included patients with an amenable mutation while BALANCE included a broader FD population, those with and without amenable mutations.
- ATTRACT trial included a wider range of eGFR values (≥ 30 mL/min/1.73 m²) compared to BALANCE, which is more specific (40-120 mL/min/1.73 m²).

6.16 There are several differences in patient characteristics that may indicate more severe FD disease in patients enrolled in the BALANCE trial compared to ATTRACT as follows, which pose transitivity issues that could confound the results of an ITC:

- Patients in the ATTRACT trial were older on average (46.3-50.5 years) compared to the BALANCE trial (45.2-43.9 years). Older patients have been associated with

more advanced/progressive FD disease,[16] which could result in a slow/limited response to therapy.

- BALANCE trial had a higher proportion of males, especially in the agalsidase beta group (72% male), while ATTRACT trial had a higher proportion of females (56-57%). FD has an X-linked inheritance pattern, which means that males typically have more severe manifestations of the disease compared to females.[4] This could potentially lead to a greater observed benefit from treatment in males, favouring BALANCE (pegunigalsidase alfa).
- The mean eGFR at baseline was lower in the BALANCE trial (73.5-74.2 mL/min/1.73 m²) compared to the ATTRACT trial (89.6-95.8 mL/min/1.73 m²). This suggests that BALANCE patients had more compromised kidney function at the start of the study, which may lead to increased improvements in kidney function or higher reductions in the eGFR.
- The proportion of participants using ACEi or ARBs was higher in the BALANCE trial (50-64%) compared to the ATTRACT trial (44-52%). ACEi and ARBs are commonly used in FD to manage hypertension and kidney dysfunction, particularly to slow the progression of kidney damage.[17] This can confound the assessment of efficacy of treatment against ATTRACT (migalastat).
- Patients in the BALANCE trial had previously been on ERT for a longer duration (5.4-6.4 years) compared to those in the ATTRACT trial (3.1-3.8 years). This suggests that the BALANCE population may have already experienced some degree of stabilisation or improvement in disease symptoms due to prior ERT, which could show less dramatic effects with the study drug compared to those in ATTRACT.

6.17 The duration of follow up was longer in the BALANCE trial compared to the ATTRACT trial (24 months vs 18 months). The different follow up durations of the trials may bias the comparability of pegunigalsidase alfa versus migalastat in favour of pegunigalsidase alfa given greater data maturity.

6.18 The submission proposed a noninferiority margin of -3.0 mL/min/1.73 m^2/year as the lower boundary of the confidence interval (CI) for the treatment difference of the annualised eGFR slope, which was the margin established in the BALANCE trial. This was based on a combination of the natural history of FD and published data[5,18] on the

[16] Lidove et al. (2016), 'Fabry in the older patient: Clinical consequences and possibilities for treatment', Molecular Genetics and Metabolism, Volume 118, Issue 4, 2016, Pages 319-325, https://doi.org/10.1016/j.ymgme.2016.05.009.

[17] Kim SH & Choi SJ (2023), 'Management of Hypertension in Fabry Disease'. Electrolyte Blood Press. 2023 Jun;21(1):8-17. doi: 10.5049/EBP.2023.21.1.8.

[18] Schiffmann et al, (2009), 'Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy'. Nephrol Dial Transplant. 2009 Jul;24(7):2102-11. doi: 10.1093/ndt/gfp031

impact of available treatments on renal function deterioration in FD patients. While the proposed non-inferiority margin may be reasonable, this has not yet been validated.

6.19 The TGA Delegate's Overview for pegunigalsidase alfa noted that the primary efficacy endpoint in the main efficacy study (BALANCE) was annualised change (slope) in eGFR, with a pre-specified non-inferiority margin of -3.0 mL/min/1.73 m^2/year. The Delegate's Overview stated that there remains some uncertainty regarding the validity of the non-inferiority margin in this small study population with large variability in clinical phenotype and severity of disease manifestations (TGA Delegate's Overview).

6.20 In March 2017, the PBAC noted that the proposed criterion for migalastat to be considered non-inferior to ERT was that the least squares (LS) mean annualised change in glomerular filtration rate (GFR) for migalastat was no lower than 2.2 mL/min/1.73m^2/year below the mean annualised rate of change for the ERT group, and the overlap in the 95% CIs was more than 50%. The PBAC considered that the non-inferiority criterion had not been fully justified (paragraph 7.4, migalastat, PSD, March 2017 PBAC meeting).

6.21 The submission stated that an ITC comparing pegunigalsidase alfa with migalastat was not presented due to exchangeability issues between the relevant studies: BALANCE and ATTRACT, including differences in trial populations, follow-up time (24 vs 18 months), and limited covariate data, which made it difficult to conduct a robust ITC. The submission stated that the National Institute for Health and Care Excellence (NICE) appraisal report for pegunigalsidase alfa highlighted that while an ITC is feasible as there is a connected network, significant limitations and heterogeneity in the evidence base would render any statistical analysis unreliable. The NICE committee noted that the company had not presented a comparison of pegunigalsidase alfa with migalastat and had stated in response to technical engagement that an indirect comparison was unfeasible.[19]

6.22 While conducting an ITC through the common comparator, ERT, is methodologically feasible, the studies differ in terms of study design, baseline characteristics and follow-up times as described in paragraphs 6.12, 6.13 and 6.14. These differences raise concerns regarding the assumption of transitivity. Additionally, the small sample sizes across the trials may further limit the potential for a robust and reliable analysis.

6.23 The results of ATTRACT and BALANCE are presented side-by-side for consideration (Table 4), noting the results of these studies are not comparable and should be interpreted with caution given the transitivity issues identified (paragraph 6.13). Information about these trials were extracted from the migalastat PSDs (March 2017 and March 2024 PBAC meetings), the literature and the submission where available.

[19] NICE (2023), 'Pegunigalsidase alfa for treating Fabry disease: Technology appraisal guidance', 4 October 2023, available at www.nice.org.uk/guidance/ta915

Comparative effectiveness

Direct comparison of pegunigalsidase alfa versus agalsidase beta

6.24 The results of key primary and secondary outcomes in the BALANCE trial at Week 104 (24 months) are presented in Table 4. The secondary outcomes of change from baseline in UPCR categories and change from baseline in LVMI by gender and hypertrophy status are presented in Table 5 and Table 6, respectively.

Table 4: Results of key primary and secondary outcomes of BALANCE trial (ITT population) at Week 104

Efficacy endpoint	Pegunigalsidase alfa (N = 52)	Agalsidase beta (N = 25)	Mean Difference (95% CI)[a]
PRIMARY OUTCOME			
Annualised change in eGFR slopes (mL/min/1.73 m^2/year), Median (95% CI)	-2.51 (-3.79; -1.24)	-2.16 (-3.81; -0.51)	-0.36 (-2.44; 1.73)[b]
SECONDARY OUTCOMES			
Change from baseline in Plasma Lyso-Gb3 (nM)			
n	46	22	-
mean (SE)	3.30 (1.38)	-8.74 (4.85)	NR
Percent (%) mean (SE)	10.34 (3.80)	-12.69 (4.60)	NR
Change from baseline in Urine Lyso-Gb3 (pM/mM creatinine)			
n	37	19	-
Mean (SE)	7.0 (7.7)	-11.2 (4.7)	**18.1 (0.1, 36.1)**
Percent (%) Mean (SE)	33.00 (13.19)	-16.14 (9.72)	**49.1 (16.3, 82.0)**
Change from baseline in Plasma Gb3 (nM)			
n	46	22	-
Mean (SE)	138.0 (214.4)	-81.8 (314.7)	219.8 (-549.3, 988.9)
Percent (%) Mean (SE)	4.59 (4.48)	2.69 (4.36)	1.9 (-10.6, 14.4)
Change from baseline in Mainz Severity Score Index (MSSI)			
n	46	23	-
Mean (SE)	-2.07 (0.77)	2.04 (1.10)	**-4.11 (-6.8, -1.4)**
Change from baseline in BPI			
n	45	22	-
Pain at its Worst in Last 24 Hours, Mean (SE)	-0.1 (0.5)	0.6 (0.6)	-0.7 (-2.2, 0.8)
Pain on Average, Mean (SE)	0.4 (0.3)	0.2 (0.4)	0.2 (-0.9, 1.2)
Change from baseline in EQ-5D-5L overall health score			
n	46	22	-
Mean (SE)	2.0 (1.9)	1.2 (3.5)	0.8 (-7.2, 8.8)
Fabry clinical events (FCE), n (%)			
Overall[c]	9 (17.3)	2 (8.0)	NR
Cardiac events[d]	6 (11.5)	2 (8.0)	NR
Cerebrovascular events[e]	3 (5.8)	0	NR
Renal events[f]	1 (1.9)	0	NR
Non-cardiac related death	0	0	NR

Source: Table 2.5-1, p65, Table 2.5-8, p71, Table 2.5-9, p72, Table 2.5-10, p73, Table 2.5-11, pp73-74, Table 2.5-12, p75, Table 2.5-13, p75, Table 2.5-14, pp76-77 of the submission.

Abbreviations: BPI, Brief Pain Inventory; CI, confidence interval; eGFR, estimated Glomerular Filtration Rate; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FCE, Fabry clinical events; Gb3, globotriaosylceramide; ITT, intention-to-treat; mL, millilitre; mM, millimolar; MSSI, Mainz Severity Score Index; nM, nanomolar; pM, picomolar; NR, not reported; SE, standard error; UPCR, Urinary Protein/Creatinine Ratio.

Note: **Bold** indicates a statistically significant difference between the treatment groups.

[a] Pegunigalsidase alfa vs agalsidase beta.

[b] Analysis was based on a quantile regression for the median with eGFR slope of each individual patient as dependent variable and treatment arm as covariate of the model. All observations are used including unscheduled visits. For non-inferiority to be indicated, the lower limit of the 95% CI had to be greater than the prespecified non-inferiority margin of -3.0. With -2.444, this criterion was met; hence, non-inferiority was shown for the ITT set.
[c] 11 events reported in nine patients in the pegunigalsidase alfa arm and two events reported in two patients in the agalsidase beta arm
[d] Seven events reported in six patients in the pegunigalsidase alfa arm and two events reported in two patients in the agalsidase beta arm
[e] Three events reported in three patients in the pegunigalsidase alfa arm
[f] One event reported in one patient in pegunigalsidase alfa

Table 5: Change from baseline to Week 104 in UPCR categories in BALANCE (ITT set)

Post baseline UPCR categories	Baseline UPCR categories							
	UPCR ≤ 0.5 gr/gr, n (%)		0.5 < UPCR < 1 gr/gr, n (%)		UPCR≥ 1 gr/gr, n (%)		Overall n (%)	
Pegunigalsidase alfa (N = 52)								
UPCR ≤ 0.5 gr/gr	31	(86.10)	3	(33.30)	0	-	34	(65.4)
0.5 < UPCR < 1 gr/gr	1	(2.80)	3	(33.30)	1	(14.30)	5	(9.6)
UPCR ≥ 1 gr/gr	0	-	1	(11.10)	5	(71.40)	6	(11.5)
Missing	4	(11.10)	2	(22.20)	1	(14.30)	7	(13.5)
Overall	36	(100.0)	9	(100.0)	7	(100.0)	52	(100.0)
Agalsidase beta (N = 25)								
UPCR ≤ 0.5 gr/gr	18	(90.0)	0	-	0	-	18	(72.0)
0.5 < UPCR < 1 gr/gr	1	(5.0)	1	(50.00)	0	-	2	(8.0)
UPCR ≥ 1 gr/gr	0	-	1	(50.00)	3	(100.0)	4	(16.0)
Missing	1	(5.0)	0	-	0	-	1	(4.0)
Overall	20	(100.0)	2	(100.0)	3	(100.0)	25	(100.0)

Source: Table 2.5-3, p67 of the submission.
Abbreviations: ITT, intention-to-treat; gr, gram; UPCR, urinary protein to creatinine ratio.

Table 6: Change from baseline in LVMI (g/m²) by gender and hypertrophy status at Week 104 in BALANCE (ITT set)

	Pegunigalsidase alfa		Agalsidase beta	
	Male, N = 29	Female, N = 23	Male, N = 18	Female, N = 7
Change from baseline in LVMI for patients with hypertrophy at baseline				
n	5	4	5	2
Mean (SE)	-2.410 (8.511)	-6.523 (8.557)	5.000 (13.274)	-4.040 (11.090)
Mean difference (95% CI) in males[a]	-7.410* (-44.904, 30.084)			
Mean difference (95% CI) in females[a]	-10.563* (-56.257, 51.292)			
Change from baseline in LVMI for patients without hypertrophy at baseline				
n	8	11	7	5
Mean (SE)	-1.344 (5.768)	2.820 (3.025)	0.987 (2.740)	-3.682 (4.716)
Mean difference (95% CI) in males[a]	-2.427* (-16.573, 11.912)			
Mean difference (95% CI) in females[a]	6.502* (-6.582, 19.586)			

Source: Table 2.5-5, p69 of the submission.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LVMI, Left Ventricular Mass Index; SE, standard error.
[a] The mean differences between pegunigalsidase alfa and agalsidase beta for males and females were not reported in the submission or BALANCE CSR, however 95% CI were presented.
*Mean differences were calculated during the evaluation.

6.25 The results of the primary outcome of annualised median eGFR slope at 24 months decreased in both the pegunigalsidase alfa arm (-2.51; 95%CI: -3.79; -1.24) and the agalsidase beta arm (-2.16; 95% CI: -3.81; -0.51), although there was no statistically significant difference between pegunigalsidase alfa and agalsidase beta (-0.36; 95% CI: -2.44, 1.73). The lower limit of the CI met the prespecified non-inferiority margin of -3.0 mL/min/1.73 m^2/year, noting this has not been validated. According to a European expert consensus statement on therapeutic goals in FD, stabilisation of kidney function is achieved if a patient has a GFR slope loss ≤1–3 mL/min/1.73 m^2/year

and progression or deterioration of renal disease is demonstrated by an annual decrease in GFR > 3 mL/min/1.73 m^2.[5] These results suggest that patients remained clinically stable in regard to kidney function.

6.26 At Week 104, all three biomarkers of FD: mean plasma lyso-Gb3, urine lyso-Gb3 and plasma Gb3 concentrations increased from baseline in the pegunigalsidase alfa arm by 3.30 nM, 7.0 pM/mM creatinine and 138.0 nM, respectively, and decreased from baseline in the agalsidase beta arm by 8.74 nM, 1.2 pM/mM creatinine and 81.8 nM, respectively. There was a statistically significant difference in the mean urine lyso-Gb3 between pegunigalsidase alfa and agalsidase beta (18.1; 95% CI: 0.1, 36.1), however this was not observed for plasma lyso-Gb3 and plasma Gb3. The submission stated that neither change in plasma lyso-Gb3, urine lyso-Gb3 and plasma Gb3 was considered clinically significant. MCIDs were not proposed for these outcomes. These biomarkers are usually elevated in patients with FD. The therapeutic goal for plasma lyso-Gb3 and plasma Gb3 is to reduce levels as much as possible, ideally to (near-) normal values, while no goal has yet been established for urine lyso-Gb3.[18] Overall, the urine lyso-Gb3 results favour agalsidase beta, and no major differences between pegunigalsidase alfa and agalsidase beta were observed in plasma lyso-Gb3 and plasma Gb3.

6.27 In terms of symptoms of FD, the results from MSSI Scores showed a mean decrease in the pegunigalsidase alfa arm (improvement by 2.07 points) and a mean increase in the agalsidase beta arm (2.04 points), which was a statistically significant difference between the two arms (-4.11; 95% CI: -6.8, -1.4) in favour of pegunigalsidase alfa. The mean difference in change from baseline in BPI for Pain at Its Worst in Last 24 Hours and for Pain on average were -0.7 (95% CI: -2.2, 0.8) and 0.2 (95% CI: -0.9, 1.2), respectively, indicating that these parameters did not change markedly over the treatment period. Similarly, the mean difference in change from baseline in EQ-5D-5L overall health score between pegunigalsidase alfa and agalsidase beta was small or not significant (0.8 [95% CI: -7.2, 8.8)].

6.28 In terms of FCE, a higher proportion of patients experienced a FCE in the pegunigalsidase alfa arm compared to the agalsidase beta arm (17.9% vs 8.0%), mainly due to cardiac events (11.5% vs 8.0%). All patients (in both arms) who developed FCEs had either suffered a similar event when untreated or were receiving treatment with agalsidase beta prior to study enrolment or had signs/symptoms of organ damage at study start (BALANCE CSR). The submission stated that these findings reflect pre-existing organ involvement in ERT-experienced patients and do not allow any conclusions to be drawn on the effect of changing to a new ERT. However, there were more FCEs in the pegunigalsidase alfa arm, favouring agalsidase beta.

6.29 The UPCR results at 24 months showed a deterioration in category for two patients (2.8%) in the pegunigalsidase alfa arm; one patient moved from mild (UPCR ≤0.5 gr/gr) to moderate (0.5 < UPCR < 1 gr/gr) and one patient moved from moderate to severe (UPCR ≥1 gr/gr) between baseline and Week 104. In the same timeframe, four patients (7.7%) improved their UPCR category. In the agalsidase beta arm, a deterioration in

category was observed in two patients (8.0%) and none of the patients improved their UPCR category.

6.30 In patients who had hypertrophy at baseline, mean LVMI values slightly decreased over two years of treatment in the pegunigalsidase alfa arm (-2.410 in males and - 6.523 in females) and in females in the agalsidase beta arm (-4.040), representing an improvement, while a modest overall increase in mean LVMI was observed in males in the agalsidase beta arm (5.000). In patients without hypertrophy, both sexes demonstrated very little change from baseline. There was no statistically significant difference in mean LVMI between pegunigalsidase alfa and agalsidase beta in patients with hypertrophy (MD=-7.410; 95% CI: -44.904, 30.084 in males and MD= -10.563; 95% CI:-56.257, 51.292 in females) and patients without hypertrophy (MD=-2.427; 95% CI: -16.573, 11.912 in males and MD= -6.502; 95% CI: -6.582, 19.586 in females). Data were missing for some patients as cardiac MRI could not be performed because of COVID-19 restrictions at the hospital. Results should be interpreted with caution given the variability was high as suggested by the wide CIs and low sample sizes in the subgroups.

6.31 Overall, the results from BALANCE at 24 months met the pre-specified non-inferiority margin for annualised change in eGFR slope. While there are some concerns about the validity of the non-inferiority margin, most primary and secondary efficacy outcomes indicate similar findings between pegunigalsidase alfa and agalsidase beta, except for urine lyso-Gb3 and FCE results, which favour agalsidase beta, and MSSI results which favour pegunigalsidase alfa.

Supporting trials

6.32 Overall BRIDGE and BRIGHT results suggest that treatment-experienced patients receiving pegunigalsidase alfa (1 mg/kg Q2W in BRIDGE and 2 mg/kg Q4W in BRIGHT) for 12 months either remained stable or improved their kidney function from baseline (mean annualised eGFR slope of 4.70 mL/min/1.73 m^2/year in BRIDGE and - 2.92 mL/min/1.73m^2/year in BRIGHT), cardiac function (mean LVMI of 4.1 g/m^2 in BRIDGE), biomarkers of FD (reductions in mean plasma lyso-Gb3 [-14.31], urine lyso-Gb3 [-17.2] and plasma Gb3 concentrations in BRIDGE and an increase in plasma lyso-Gb3 [3.01] and plasma Gb3 [334.22] in BRIGHT with urine lyso-Gb3 decreasing [-0.66] by 12 months), symptoms of FD (mean MSSI decreased in both BRIDGE [-0.1] and BRIGHT [-0.2]) and QoL (mean EQ-5D-5L overall health score increased in BRIDGE [5.1] and BRIGHT [3.0]). These results are consistent with BALANCE, except for LVMI, which slightly increased but still remained within normal ranges, and biomarkers of FD, which decreased, suggesting better improvements than BALANCE.

6.33 The PB-102-F01, PB-102-F02 and PB-102-F03 are single arm studies with small sample sizes and the results suggest that treatment-naïve patients receiving pegunigalsidase alfa (1 mg/kg Q2W) for up to 60 months (five years) remained stable in their annualised eGFR slope (reduction ≤1–3 mL/min/1.73m^2/year), and improved (decreased) mean plasma lyso-Gb3, plasma Gb3 and kidney Gb3 (BLISS scores)

concentrations from baseline. These results are consistent with the BALANCE trial findings.

6.34 The TGA Delegate's Overview indicated that findings from PB-102-F20 (BALANCE) are supported by favourable pharmacodynamics (PD) findings in treatment-naïve participants in Study PB-102-F01/02, including reductions in plasma lyso-Gb3 concentrations and mean BLISS scores following treatment with pegunigalsidase alfa (Delegate's Overview).

Additional summary of BALANCE and ATTRACT trials

6.35 Table 7 presents the results of the primary endpoint of annualised change in eGFR slope in BALANCE and ATTRACT trials. The results are presented side-by-side for ease of comparison; however, the results of these studies are not comparable and should be interpreted with caution given the transitivity issues identified (see paragraph 6.19).

Table 7: Results of primary endpoint of annualised change in eGFR slope in BALANCE and ATTRACT trials

	BALANCE study[a]			ATTRACT study[b]		
	Pegunigalsidase alfa LS mean change (95% CI)	ERT LS mean change (95% CI)	Mean difference (95% CI)	Migalastat LS mean change (SE)	ERT LS mean change (SE)	Mean difference (95% CI)
ITT	-2.37 (-3.64, -1.09)	-2.31 (-4.09, -0.53)	-0.59 (-2.25, 2.13)	-0.23 (1.12)	-2.85 (1.46)	2.62 (-0.99, 6.23)
mITT amenable	NR	NR	NR	-0.40 (0.93)	-1.03 (1.29)	0.63 (-2.49, 3.75)

Source: Table 2.6.3, p99 of the submission and Table 3, migalastat, PSD, March 2017 PBAC meeting.

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; LS, least square; mITT, modified intention to treat; NR, not reported; SE, standard error.

[a] Estimated mean eGFR slopes using random intercept random slope (RIRS) longitudinal mixed model reported as sensitivity analysis in Table 11.11 of the BALANCE CSR at 24 months. BALANCE results in section 2.5 of the submission and Table 4, were reported as median rather than mean changes.

[b] Results reported at 18 months.

Note: ATTRACT and BALANCE results correspond to eGFR CKD-EPI, glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

6.36 The LVMI results for the mITT population and a subgroup of patients with left ventricular hypertrophy (LVH) at baseline in the ATTRACT trial are presented in Table 8. The LVMI results of the BALANCE trial were not reproduced below given these have already been presented in Table 6, but a description is included.

Table 8: Results of secondary outcome in ATTRACT: Change in LVMI from baseline

	ATTRACT [Treatment experienced] at 18 months			
	MIG N=36	ERT N=24	MIG N=36	ERT N=24
Analysis group	mITT amenable		Subgroup: LVH baseline	
LVMI (g/m^2)	n=34	n=13	n=13	n=5
Mean change (SD)	-6.6 (12.08)	−2.0 (14.86)	-8.4 (10.67)	4.5 (20.45)
95% CI	-11.01, -2.15	-10.99, 6.96	-15.69, 2.56	-10.71, 18.43
Mean diff (95% CI)	-4.60 (-13.97, 4.77) p=NS		-12.90 (-31.99, 6.19) p=NS	

Source: Table 5 of migalastat, PSD, March 2017 PBAC meeting

Abbreviations: CI, confidence interval; diff, difference; ERT, enzyme replacement therapy; LVH, left ventricular hypertrophy; LVMI, Left Ventricular Mass Index; MIG, migalastat; N, number; NS, not significant; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; SD, standard deviation.

Note: Mean differences were calculated post hoc.

6.37 In ATTRACT, the mean difference in LVMI between the migalastat group and ERT group was not statistically significant for the mITT population (mean difference: -4.60; 95% CI: -4.77, 13.97) or LVH subgroup (mean difference: -12.90; 95% CI: -31.99, 6.19). The sample size for patients with LVH at baseline was further reduced from the overall sample, and based on the available data, it was unclear if treatment with migalastat resulted in a reduction in LVMI in patients with LVH at baseline compared with those in the mITT amenable population (paragraph 6.15, migalastat, PSD, March 2017 PBAC meeting).

6.38 At its March 2017 consideration of migalastat, the PBAC did not accept the submission's claim that, based on the change in LVMI, migalastat was superior to ERT in reducing LVMI in Fabry patients. The PBAC recalled that it has previously considered the clinical relevance of left ventricular mass as an outcome in Fabry patients to be uncertain (paragraph 7.5, migalastat, PSD, March 2017 PBAC meeting).

6.39 In BALANCE, there was no statistically significant difference in mean LVMI between pegunigalsidase alfa and agalsidase beta in patients with hypertrophy (MD=-7.410; 95% CI: -44.904, 30.084 in males and MD= -10.563; 95% CI:-56.257, 51.292 in females) and patients without hypertrophy (MD=-2.427; 95% CI: -16.573, 11.912 in males and MD= -6.502; 95% CI: -6.582, 19.586 in females). Noting that there was a high variability as suggested by the wide CIs and low sample sizes in the subgroups.

6.40 Overall, both BALANCE and ATTRACT trials showed no significant differences in terms of annualised change in eGFR slope and change in LVMI between respective drugs, noting the small sample sizes.

Comparative harms

Direct comparison of pegunigalsidase alfa versus agalsidase beta

6.41 The key safety outcomes occurring in patients treated with pegunigalsidase alfa versus agalsidase beta in the BALANCE trial are summarised in Table 9. Figure 1 shows the rates of patients who tested positive for anti-drug antibodies (ADAs) and neutralising antibodies to their respective treatment over time in the BALANCE trial. A description of the use of infusion premedication was presented in the submission and is included below.

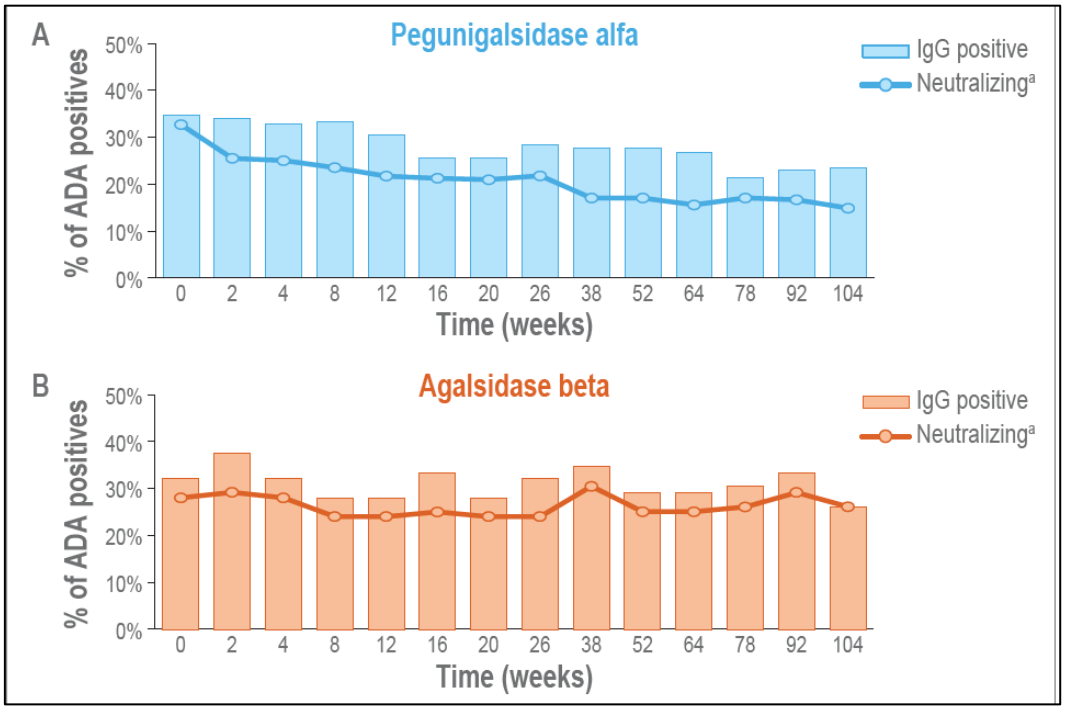
Table 9: Summary of key safety outcomes of pegunigalsidase alfa vs agalsidase beta in BALANCE

	Pegunigalsidase alfa (N = 52)		Agalsidase beta (N = 25)	
	Number of patients with at least one event, n (%)	Number of events (rate)[a]	Number of patients with at least one event, n (%)	Number of events (rate)[a]
All TEAEs				
Any TEAE	47 (90.4)	561 (572.36)	24 (96.0)	406 (816.85)
Mild or moderate TEAE	47 (90.4)	535 (545.83)	24 (96.0)	387 (778.63)
Severe TEAE[b]	15 (28.8)	26 (26.53)	7 (28.0)	19 (38.23)
Any SAE	8 (15.4)	14 (14.28)	6 (24.0)	11 (22.13)
TEAE leading to withdrawal	2 (3.8)	2 (2.04)	0	0
TEAE leading to death	0	0	0	0
Related TEAEs only				
Any related TEAE[c]	21 (40.4)	42 (42.85)	11 (44.0)	76 (152.91)
Related mild or moderate TEAE	21 (40.4)	40 (40.81)	11 (44.0)	75 (150.90)
Related severe TEAE	2 (3.8)	2 (2.04)	1 (4.0)	1 (2.01)
Related serious TEAE	1 (1.9)	1 (1.02)	0	0
Related TEAE leading to withdrawal	1 (1.9)	1 (1.02)	0	0
Related TEAE leading to death	0	0	0	0
TEAEs in ≥10% of patients in either treatment group				
Nasopharyngitis	11 (21.2)	21 (21.4)	4 (16.0)	6 (12.1)
Headache	11 (21.2)	19 (19.4)	5 (20.0)	9 (18.1)
Diarrhoea	10 (19.2)	15 (15.3)	6 (24.0)	10 (20.1)
Nausea	9 (17.3)	10 (10.2)	3 (12.0)	3 (6.0)
Fatigue	9 (17.3)	10 (10.2)	4 (16.0)	6 (12.1)
Back pain	8 (15.4)	12 (12.2)	5 (20.0)	6 (12.1)
Proteinuria	6 (11.5)	7 (7.1)	0	0
Cough	6 (11.5)	7 (7.1)	5 (20.0)	7 (14.1)
Bronchitis	5 (9.6)	6 (6.1)	5 (20.0)	7 (14.1)
SAEs by system organ class (SOC)				
Cardiac disorders	1 (1.9)	1 (1.0)	3 (12.0)	3 (6.0)
Atrioventricular block second degree	1 (1.9)	1 (1.0)	0	0
Atrial fibrillation	0	0	1 (4.0)	1 (2.0)
Tachycardia	0	0	1 (4.0)	1 (2.0)
Ventricular tachycardia	0	0	1 (4.0)	1 (2.0)
General disorders and administration site conditions	1 (1.9)	1 (1.0)	2 (8.0)	2 (4.0)
Hypothermia	1 (1.9)	1 (1.0)	0	0
Chest pain	0	0	2 (8.0)	2 (4.0)
IRR occurring within 2 hours of infusion				
Any IRR	11 (21.2)	13 (0.50)	6 (24.0)	51 (3.9)
Severe IRR	1 (1.9)[d]	1 (0.0)	0	0
Serious IRR	1 (1.9)[d]	1 (0.0)	0	0
IRR leading to withdrawal	1 (1.9)[d]	1 (0.0)	0	0

Source: Table 2.5-15, Table 2.5-16, Table 2.5-17, Table 2.5-18, pp86-90 of the submission.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; eCRF, electronic case report form; IRR, infusion-related reaction; SAE, serious adverse event; SE, standard error; SOC, system organ class; TEAE, treatment-emergent adverse event.
[a] Rate is calculated as the adjusted number of events per 100 years of exposure for all TEAEs and SAEs and per 100 infusions for IRRs. Total cumulative exposure was 1176.2 months in the pegunigalsidase alfa arm (N = 52) and 596.4 months in the agalsidase beta arm (N = 25), with similar means (SE) between the treatment groups for individual exposure: 22.62 (0.72) versus 23.86 (0.27) months, respectively.

[b] Events classified as "Very Severe" per CTCAE severity in the eCRF are included in the category "Severe".
[c] A TEAE was defined as related if was reported as possibly, probably, or definitely related to study drug.
[d] One serious IRR, one severe IRR (hypersensitivity) and one IRR leading to withdrawal was reported in the same patient in the pegunigalsidase alfa arm.

Figure 1: Rates of ADA-positive patients and ADA-positive patients with neutralising antibodies over time in BALANCE



Source: Figure 2.5-8, p91 of the submission and Wallace et al. 2023 poster.
Abbreviations: ADA, antidrug antibody; IgG, immunoglobulin G; nAb+, positive for neutralising antibodies.
[a] Proportion (%) of nAb+ calculated out of total patients in respective treatment arm.

6.42 The proportion of patients with at least one TEAE, serious TEAE and related TEAE in pegunigalsidase alfa (90.4%, 15.4% and 40.4% respectively) was lower compared to agalsidase beta (96%, 24% and 44% respectively), with the rate of events adjusted for exposure being notably lower in any TEAE (572.36 per 100 patient-years of exposure in pegunigalsidase alfa vs 816.85 per 100 patient-years of exposure in agalsidase beta) and any related TEAE (42.85 per 100 patient-years of exposure in pegunigalsidase alfa vs 152.91 per 100 patient-years of exposure in agalsidase beta). One patient in the pegunigalsidase alfa arm discontinued from the study due to TEAE that were considered related to study treatment (hypersensitivity), and no patients discontinuing due to TEAE were reported in the agalsidase beta arm.

6.43 Among the pegunigalsidase alfa patients, the most common types of TEAEs were nasopharyngitis and headache (21.2% each), diarrhoea (19.2%), and nausea and fatigue (17.3% each). Among the agalsidase beta patients, the most common TEAEs were diarrhoea (24%), and headache, back pain, cough, and bronchitis (20.0% each). TEAEs more frequently observed (>10% difference) in the agalsidase beta arm compared to pegunigalsidase alfa included: abdominal pain upper (16% vs 3.8%), blood creatinine increased (16% vs 3.8%), paraesthesia (16% vs 3.8%), abdominal

discomfort (12% vs 1.9%), chest pain (12% vs 1.9%), influenza like illness (12% vs 1.9%), pharyngitis (16% vs 1.9%), fall (12% vs 1.9%), rhinorrhoea (12% vs 1.9%), pruritus (12% vs 0), and gastroenteritis (12% vs 0). Abdominal pain and proteinuria (11.5% each) were more frequently seen in pegunigalsidase alfa while none of these TEAEs were reported in agalsidase beta (0% each).

6.44 More patients in the agalsidase beta arm compared with the pegunigalsidase alfa arm (difference by >5% of patients) reported cardiac disorder serious AEs (SAEs) (12.0% vs 1.9%, respectively) and general disorder SAEs (8.0% vs 1.9%, respectively). Other SAEs were similar between treatment arms.

6.45 A lower rate of infusion-related reactions (IRRs) was reported in pegunigalsidase alfa compared to agalsidase beta (21.2% [0.5 per 100 infusions] versus 24.0% [3.9 per 100 infusions]) within 2 hours of completing the infusion. However, there was one serious IRR, one severe IRR (hypersensitivity) and one IRR leading to withdrawal reported in the same patient in the pegunigalsidase alfa arm and none in the agalsidase beta arm. There were more FCE events in the pegunigalsidase alfa arm (17.3% vs 8.0%) including cardiac, cerebrovascular and renal events that were not captured as AEs.

6.46 Treatment-emergent ADA, defined as either going from ADA negative at baseline to ADA positive post-baseline or experiencing a greater than fourfold post-baseline increase in immunoglobulin G (IgG) titre, was reported in less patients in the pegunigalsidase alfa arm (n=6 [11.5%]) compared to the agalsidase beta arm (n=5 [20.0%]). Of the patients who were ADA positive at baseline (n = 18 [35%] for pegunigalsidase alfa, n = 8 [32%] for agalsidase beta), all except 1 in each arm (94.4% and 87.5%, respectively) were positive for neutralising antibodies as well. Of the patients who were ADA positive at Week 104 (n = 11 [23%] and n = 6 [26%], respectively), 7 (63.3%) and 6 (100%) patients in the pegunigalsidase alfa arm and agalsidase beta arm were still positive for neutralising antibodies as well (i.e., this percentage decreased in the pegunigalsidase alfa arm whereas remained stable in the agalsidase beta arm). The submission stated that this finding of low treatment-emergent immunogenicity and increased tolerisation is important not only from a safety perspective, but also with respect to efficacy, as antibodies developed against an ERT product, especially neutralising antibodies, would be expected to inhibit its activity and potentially adversely affect the clinical outcome.

6.47 At the end of the study, neutralising antibodies (or ADAs) were detected in 7 out of 47 (15%) pegunigalsidase alfa-treated patients and 6 out of 23 (26%) agalsidase beta-treated patients (Wallace et al., 2024).[20] There is some evidence that ADAs are

[20] Wallace et al, (2024), 'Head-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomised phase III BALANCE study'. J Med Genet. 2024 May 21;61(6):520-30. doi: 10.1136/jmg-2023-109445.

linked to reducing efficacy and increasing complications of FD (Lenders et al., 2018[21]; Torra R., 2008[22]; Mauhin et al., 2018[23]).

6.48 The recommendation to use premedications proactively to prevent reactions to agalsidase beta was challenged during the study, and in many cases, premedications were successfully reduced or discontinued based on the patient's tolerance. At baseline, premedications were taken by 20 (38.5%) pegunigalsidase alfa-treated patients versus 15 (60.0%) agalsidase beta-treated patients. Over the course of the study, premedication use decreased in both treatment arms but more so in the pegunigalsidase alfa arm, which the submission stated indicated better tolerability. At Week 104, infusion premedications were taken by three (6.4%) patients in the pegunigalsidase alfa arm and three (12.0%) patients in the agalsidase beta arm. The submission stated this indication of greater tolerability is consistent with the lower rate of IRRs seen in the pegunigalsidase alfa arm, described above. However, as described in paragraph 6.42, there was one serious IRR, one severe IRR (hypersensitivity) and one IRR leading to withdrawal reported in the same patient in the pegunigalsidase alfa arm and none in the agalsidase beta arm.

6.49 Overall, the safety profile of pegunigalsidase alfa is comparable/similar to agalsidase beta, and most frequently reported AEs are described in the draft PI. Although the submission claimed that pegunigalsidase alfa has a reduced risk of immunogenicity, the risk of developing treatment-induced ADAs still exists and is reflected in the draft PI for pegunigalsidase alfa.

6.50 The submission claimed that pegunigalsidase alfa is non-inferior to agalsidase beta in terms of efficacy, providing an alternative option for both ERT-naïve and ERT-experienced patients, with an improved safety profile and reduced immunogenicity compared to agalsidase beta, while maintaining renal and cardiac functions. The submission stated that as the PBAC have previously deemed agalsidase alfa and agalsidase beta to be non-inferior in terms of efficacy and safety (agalsidase alfa and beta, PSD, November 2009 PBAC meeting), the claim is that as pegunigalsidase alfa is non-inferior to agalsidase beta, it is also non-inferior to agalsidase alfa in terms of efficacy and safety. This claim was inferred based on BALANCE results, and there is no direct evidence comparing pegunigalsidase alfa with agalsidase alfa. At its November 2009 meeting, the PBAC considered there was insufficient evidence to support a finding that there is any clinical difference between the agalsidase alfa and agalsidase beta (Section 8, Updated literature review of agalsidase alfa (Replagal®) and

[21] Lenders et al, (2018), 'Dose-Dependent Effect of Enzyme Replacement Therapy on Neutralizing Antidrug Antibody Titers and Clinical Outcome in Patients with Fabry Disease', J Am Soc Nephrol. 2018 Dec;29(12):2879-89. doi: 10.1681/ASN.2018070740.

[22] Torra R., (2008), 'Renal manifestations in Fabry disease and therapeutic options', Kidney Int Suppl. 2008 Dec;(111):S29-32. doi: 10.1038/ki.2008.522.

[23] Mauhin et al, (2018), 'Deep characterization of the anti-drug antibodies developed in Fabry disease patients, a prospective analysis from the French multicenter cohort FFABRY'. Orphanet J Rare Dis 13, 127. https://doi.org/10.1186/s13023-018-0877-4

agalsidase beta (Fabrazyme®) for the treatment of Fabry disease, PSD, November 2009 PBAC meeting).

Supporting trials

6.51 The submission presented a description of the safety outcomes of BRIDGE and BRIGHT only to support the safety claim of BALANCE. Overall, the safety data from BRIDGE and BRIGHT are generally consistent with the safety profile demonstrated for pegunigalsidase alfa in BALANCE, showing similar proportions of TEAEs (95.5% in BRIDGE and 90% in BRIGHT) and IRRs (13.6% in BRIDGE) that were mild/moderate and resolved during the study, and a decreasing trend in the use of premedication overtime (from 26.7% at baseline to 13.8% at Week 52 in BRIGHT).

Additional summary of BALANCE and ATTRACT trials

6.52 Table 10 provides a summary of the adverse events of the BALANCE and ATTRACT trials.

Table 10: Summary of adverse events in the BALANCE and ATTRACT trials

AEs	BALANCE [Treatment experienced] (24 months)		ATTRACT [Treatment experienced] (18 months)	
	Pegunigalsidase N=52	ERT N=25	Migalastat N=36	ERT N=24
Safety Population subjects, n	52	25	36	21
TEAEs (number of events)	561	406	308	166
TEAEs, subjects, n (%)	47 (90)	24 (96)	34 (94)	20 (95)
Related TEAEs[a], subjects, n (%)	21 (40)	11 (44)	14 (39)	3 (14)
Severe TEAEs, subjects, n (%)	15 (29)	7 (28)	3 (8)	2 (10)
Treatment-Emergent SAEs, subjects, n (%)	1 (2)	0	7 (19)	7 (33)
Discontinued due to TEAEs, subjects, n (%)	1 (2)	0	0	0
AEs Leading to Death, subjects, n (%)	0	0	0	0

Source: Table 2.6-4, pp99-100 of the submission.

[a] A TEAE was defined as related if it was reported as possibly, probably, or definitely related to study drug.

Abbreviations: AE; adverse event; ERT; enzyme replacement therapy; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

6.53 Although the two trials had different study designs, including the study timeframe and participant numbers, the proportion of patients with TEAEs in BALANCE was comparable (90%) in the pegunigalsidase alfa arm versus agalsidase beta (96%) and between migalastat (94%) and ERT (95%) in ATTRACT.

6.54 A higher percentage of severe TEAEs was observed in pegunigalsidase alfa in BALANCE (29%) compared with migalastat in ATTRACT (8%), however, treatment emergent SAEs were lower in the pegunigalsidase alfa (2%) in the BALANCE study compared with agalsidase beta (19%) in ATTRACT. Only 1 (2%) patient in the pegunigalsidase alfa arm discontinued due to a TEAE in BALANCE versus none in the agalsidase beta arm in ATTRACT. In both BALANCE and ATTRACT, there were no AEs that led to death.

6.55 The most commonly reported TEAEs in ATTRACT after 18 months were nasopharyngitis (both migalastat and ERT 33%) and headache (migalastat 25%; ERT 24%). Dizziness (17%), abdominal pain (14%), diarrhoea (14%) and nausea (14%) were more frequently seen in the migalastat group than in the ERT group. TEAEs more

frequently observed in the ERT group compared to migalastat included: influenza (19% vs 14%), cough (24% vs 8%), back pain (14% vs 11%), bronchitis (14% vs 6%), vomiting (14% vs 8%) and sinusitis (14% vs 8%) (paragraph 6.18, migalastat, PSD, March 2017 PBAC meeting). As described in paragraph 6.40, nasopharyngitis, headache, diarrhoea and nausea were also commonly reported in the pegunigalsidase alfa arm in BALANCE.

6.56 A higher proportion of nasopharyngitis (33% vs 21.2%), headache (25% vs 21.2%), dizziness (17% vs 11.5%) and abdominal pain (14% vs 11.5%) was observed with migalastat in ATTRACT compared with pegunigalsidase alfa in BALANCE, while a higher rate of diarrhoea (19.2% vs 14%) and nausea (17.3% vs 14%) was observed with pegunigalsidase alfa than with migalastat.

6.57 The submission acknowledged that the PBAC previously concluded at its March 2024 meeting that there was insufficient evidence to definitively establish non-inferiority in terms of clinical effectiveness of migalastat compared to ERTs (agalsidase alfa and agalsidase beta) (paragraph 7.6, migalastat, PSD, March 2024 PBAC meeting). The submission stated that as the clinical claim for pegunigalsidase alfa is non-inferior in efficacy to agalsidase alfa and agalsidase beta, the clinical claim versus migalastat is that pegunigalsidase alfa has at least non-inferior efficacy to migalastat. The submission stated that in terms of safety, it would appear that migalastat and pegunigalsidase alfa have a quantitatively similar safety profile (submission). There is no direct evidence comparing pegunigalsidase alfa with migalastat and the submission did not present robust indirect evidence to support the claims of non-inferior efficacy and safety over migalastat.

6.58 Based on the PBAC's previous considerations of migalastat, the PBAC considered it reasonable to accept the claim of non-inferior comparative safety compared to ERT (paragraph 7.8, migalastat, PSD, March 2017 PBAC meeting). In terms of clinical effectiveness, the PBAC considered that despite the availability of longer-term clinical data for ATTRACT and FACETS, the claim that migalastat is non-inferior to ERT remained insufficient (paragraph 7.6, migalastat, PSD, March 2024 PBAC meeting).

Benefits/harms

6.59 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.60 The submission described pegunigalsidase alfa as non-inferior to both agalsidase alfa and agalsidase beta in terms of efficacy and safety, providing an alternative option for both ERT-naïve and ERT-experienced patients. The claim of non-inferior efficacy and safety over agalsidase beta is adequately supported, however the claim against agalsidase alfa remains uncertain due to the lack of clinical evidence comparing pegunigalsidase alfa with agalsidase alfa. The claim against agalsidase alfa was inferred based on BALANCE results and the claim that the PBAC had previously considered agalsidase alfa and agalsidase beta to be non-inferior in terms of efficacy and safety. In November 2009, the PBAC considered there was insufficient evidence to support a finding that there is any clinical difference between agalsidase alfa and agalsidase beta (Section 8, Updated literature review of agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®) for the treatment of Fabry disease, PSD, November 2009 PBAC meeting).

- Overall, the results from BALANCE at 24 months met the pre-specified non-inferiority margin for annualised change in eGFR slope. While there are some concerns about the validity of the non-inferiority margin, the primary and secondary efficacy outcomes indicate similar findings between pegunigalsidase alfa and agalsidase beta, except for urine lyso-Gb3 and FCE results, which favour agalsidase beta, and MSSI results which favour pegunigalsidase alfa.
- While the supporting trials BRIDGE, BRIGHT, PB-102-F01, PB-102-F02 and PB-102-F03 are single arm studies with small sample sizes, the results suggest that treatment-experienced and treatment-naïve patients receiving pegunigalsidase alfa either remained stable or had improved their kidney function (annualised eGFR slope), cardiac function (LVMI), biomarkers of FD including plasma lyso-Gb3, urine lyso-Gb3, plasma Gb3 and kidney Gb3 concentrations, symptoms of FD and QoL. These results support BALANCE findings.
- The safety profile of pegunigalsidase alfa is similar to agalsidase beta with most frequently reported AEs being described in the draft PI. Although the submission claimed that pegunigalsidase alfa has reduced risk of immunogenicity, the risk of developing treatment-induced ADAs still exists and is reflected in the draft PI for pegunigalsidase alfa.
- The safety data from the supporting studies BRIDGE and BRIGHT are generally consistent with the safety profile demonstrated with pegunigalsidase alfa in BALANCE, showing similar proportions of TEAEs and IRRs that were mild/moderate and resolved during the study, and a decreasing trend in the use of premedication overtime.
- However, the claim against agalsidase alfa was inferred based on BALANCE results and the claim that the PBAC had previously considered agalsidase alfa and agalsidase beta to be non-inferior in terms of efficacy and safety. In November 2009, the PBAC considered there was insufficient evidence to support a finding

that there is any clinical difference between agalsidase alfa and agalsidase beta (Section 8, Updated literature review of agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®) for the treatment of Fabry disease, PSD, November 2009 PBAC meeting). There is no direct evidence comparing pegunigalsidase alfa with agalsidase alfa.

6.61 The submission described pegunigalsidase alfa as at least non-inferior in terms of effectiveness with a similar safety profile to migalastat. This claim is uncertain and not adequately supported by the available evidence because:

- There is no direct evidence comparing pegunigalsidase alfa with migalastat and the submission did not present an ITC or robust evidence to support this claim. The differences between the BALANCE and ATTRACT studies in study design, baseline characteristics and follow up times raised concerns regarding the assumption of transitivity, limiting the potential for a robust and reliable ITC.

6.62 The PSCR and pre-PBAC response acknowledged differences in trial populations, follow-up time, and limited covariate data across the BALANCE and ATTRACT trials could make ITC comparing pegunigalsidase alfa with migalastat misleading and stated that a clinical claim for pegunigalsidase alfa versus migalastat is problematic. The PSCR stated that issues with undertaking a valid ITC between migalastat and ERT were also recognised by the PBAC at its March 2017 consideration of migalastat. They additionally noted the PBAC's consideration of migalastat at its March 2024 meeting and that the claim that migalastat had non-inferior effectiveness compared to ERT was considered uncertain. The PCSR claimed that this suggests that migalastat may have lower efficacy than ERTs on the LSDP.

6.63 The ESC noted the side-by-side comparison of BALANCE and ATTRACT trials. The ESC agreed that it was reasonable for the submission not to present an ITC between pegunigalsidase alfa and migalastat given the transitivity issues identified.

6.64 The ESC noted there is no direct evidence comparing pegunigalsidase alfa with migalastat, and that for this reason the claim against migalastat remains uncertain. The ESC considered that overall, while the clinical claim for pegunigalsidase alfa against ERTs was likely plausible, there was no direct evidence provided to support the claim against agalsidase alfa.

6.65 The pre-PBAC response claimed that pegunigalsidase alfa offered comparable efficacy to the two other ERTs available, and may offer comparable or superior efficacy compared to migalastat.

6.66 The PBAC considered that the claim of non-inferior comparative effectiveness compared to agalsidase beta was reasonable. The PBAC considered the claim of non-inferior comparative effectiveness compared to agalsidase alfa was likely reasonable, however no direct evidence was provided to support this claim. The PBAC considered that the claim of non-inferior comparative effectiveness compared to migalastat was supported by the data, with a high level of uncertainty.

6.67 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.68 The submission did not present a cost-minimisation approach to the proposed main comparators (ERT, agalsidase alfa and agalsidase beta) claiming that both these medications are currently listed on the LSDP and have not demonstrated cost-effectiveness for PBAC consideration. The prices of agalsidase alfa and agalsidase beta on the LSDP were not known to the sponsor.

6.69 The submission instead presented a cost-minimisation approach against migalastat with a proposal seeking a [redacted]% price premium over migalastat. The submission claimed this was based on the PBAC's consideration that the migalastat efficacy claim of non-inferior efficacy against ERT was not well supported, and this was reflected in the history of FD pricing, with migalastat initially being listed on the LSDP at a lower (but unknown) price than agalsidase alfa and agalsidase beta. It would be more usual for a price premium to be supported by a superiority claim and accompanied by a full cost-effectiveness evaluation. The claim of non-inferior efficacy and safety for pegunigalsidase alfa compared to migalastat is uncertain and not adequately supported by the evidence presented (see paragraph 6.58). The absence of evidence for non-inferiority between migalastat and ERT does not constitute evidence of superiority, which would require robust clinical data to substantiate. The ESC noted that a lack of evidence demonstrating that migalastat is non-inferior to ERT does not mean ERTs have superior efficacy to migalastat and considered there was no basis to support a price premium for pegunigalsidase alfa over migalastat.

6.70 The PSCR claimed that the requested [redacted]% price premium over the estimated annual cost of migalastat accounted for the PBAC's previous consideration that migalastat has not shown non-inferior efficacy compared to ERTs, and the recommended price in relation to ERTs. The PSCR further claimed that pegunigalsidase alfa with the [redacted]% price premium would still be a lower price than that of ERTs currently on the LSDP.

6.71 The ESC did not support this proposed justification of a [redacted]% price premium over migalastat based on the pricing of migalastat on the LSDP. By definition, pricing on the LSDP is not cost-effective and hence should not come into consideration when the PBAC considers a cost-effective price. The effective price of migalastat on the PBS is the price against which a CMA of pegunigalsidase alfa to migalastat should be conducted.

6.72 The pre-PBAC response claimed that the PBAC has not accepted that migalastat is non-inferior to ERTs in past considerations, and that a formal cost-effectiveness analysis between migalastat and pegunigalsidase alfa is not possible due to the absence of direct comparison between the two medicines, and the limitations of indirect comparison. The pre-PBAC response claimed that the requested [redacted]% premium was a pragmatic approach, consistent with previous pricing differences between ERTs and migalastat.

6.73 The equi-effective doses were estimated as 78.9 mg Q2W and migalastat 123 mg every other day. As the recommended dosing of pegunigalsidase alfa is dependent on weight, the submission applied the mean weight of patients (78.9 kg) in the BALANCE trial to estimate the required dose for each administration. This is reasonable. The proposed equi-effective doses were based on the dosing and frequency of use as per the TGA approved PI for migalastat and draft PI for pegunigalsidase alfa.

6.74 The submission included administration costs associated with the infusion of IV pegunigalsidase alfa and stated that there would be no administrative costs associated with administering migalastat as it is taken orally. To account for the IV infusion costs, the submission applied a cost of $123.05 based on the Medicare Benefits Schedule (MBS) item code 13950. The MBS item (13950) applied is not appropriate as this relates to administration of antineoplastic agents. It may be appropriate to apply MBS item 116 ($87.30) as the infusion would likely be overseen by a specialist in the consulting room or hospital. This was tested during the evaluation, and it has a minimal impact on the cost-minimisation approach result (<1% difference compared to the base case presented in the submission).

6.75 In the BALANCE trial, 46% of pegunigalsidase alfa infusions were administered at home. As described in the draft PI, patients can have the infusions at home if the patient is tolerating their infusions well and have no history of moderate or severe IRRs for at least a few months.

6.76 The cost-minimisation results presented in the submission were calculated on an annual basis based on a dispensed price for maximum quantity (DPMQ) of $28,076.45 for a pack of migalastat (14 capsules of 150 mg for a 28-day supply). Based on this, the submission estimated that the AEMP of one vial of pegunigalsidase alfa is $3,477.17 and with a [redacted]% price premium, it would be $[redacted]. The submission's approach of using DPMQ for the cost calculations and then subtracting mark-up fees from the total treatment cost to estimate the AEMP per vial was not appropriate. This was corrected using the AEMP of migalastat during the evaluation which resulted in a slightly lower AEMP per vial of pegunigalsidase alfa (<1% difference) as presented in Table 11 below.

Table 11: Results of the cost-minimisation

Component	Pegunigalsidase alfa*	Migalastat
Cost per dose	$13,833.88[a]	$1,993.85
Cost per 28-day supply	$27,667.75	$27,913.85[b]
Dose duration	1 year (52.18 weeks)	1 year (52.18 weeks)
Number of vials / packs per year	104.36	13.04
Administrations per year	26.09	182.63
Total medicine cost per year	$363,036.98	$366,247.26
Total IV infusion administration cost per year	$3,210.29[c]	$0
Difference in cost per year	$0	$0
Estimated cost minimised price per vial of pegunigalsidase alfa (AEMP)	$3,458.47	
Cost minimised price with a [redacted]% premium	$[redacted]	

Source: Table 3.4-2, p111 of the submission and corrected during the evaluation

Abbreviations: AEMP, approved ex-manufacturer price; IV, intravenous; MBS, Medicare Benefits Schedule.

[a] Based on 4 vials assuming a mean body weight of 78.89 kg

[b] Published AEMP of 1 pack (14 capsules) of migalastat

[c] MBS item 13950 ($123.05)
*Added during evaluation

6.77 These results should be interpreted with caution given the lack of evidence to support the clinical claim of non-inferiority of pegunigalsidase alfa against migalastat and the doses used in the calculations.

6.78 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with pegunigalsidase alfa would be no more than the cost per patient of the lowest cost comparator. Where the cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. In this case, the PBAC should consider the following parameters: administration costs.

Pegunigalsidase alfa cost/patient/year: $[redacted]

Table 12 : Drug cost per patient per month for pegunigalsidase alfa and comparators (migalastat, agalsidase alfa and agalsidase beta) drugs

	Pegunigalsidase alfa Trial dose and duration	Pegunigalsidase alfa CMA	Pegunigalsidase alfa Financial estimates	Agalsidase beta Trial dose and duration	Migalastat CMA	Agalsidase alfa and agalsidase beta Financial estimates
Mean dose	NR	78.89 mg[b]	78.9 mg[b]	NR	123 mg	agalsidase alfa: 15.78 mg[c] agalsidase beta: 78.89 mg[c]
Treatment compliance	99.24%	100%	100%	98.95%	100%	100%
Cost/patient/ year	$[redacted][a]	$[redacted][c]	$[redacted][c]	agalsidase beta: $538,476[d]	$364,116[e]	agalsidase alfa: $490,703[f] agalsidase beta: $544,190[g]

Source: Compiled during the evaluation using BALANCE trial data; Attachment 06 Cost Analysis, Attachment 04 Financial Model.
Abbreviations: CMA, cost-minimisation approach; DPMQ, dispensed price for maximum quantity; mg, milligram; NR, not reported.
[a] Calculated based on recommended dose and mean body weight reported in the BALANCE trial (104.4 vials per year) using the submission's proposed AEMP for pegunigalsidase alfa ($[redacted]) and adjusted for compliance rate.
[b] Based on mean body weight (78.89 kg) reported in the BALANCE trial. .
[c] Calculated based on the recommended dose and mean body weight reported in the BALANCE trial (104.4 vials per year) using the submission's proposed AEMP for pegunigalsidase alfa ($[redacted]).
[d] Calculated based on the recommended dose and mean body weight reported in the BALANCE trial (52.18 vials of 5 mg and 52.18 vials of 35 mg per year) using the submission's assumed AEMP for agalsidase beta ($1,303.64 for 5 mg and $9,125.45 for 35 mg) and adjusted for compliance rate.
[e] Calculated using migalastat AEMP ($27,913.85) and number of scripts (13.04).
[f] Calculated based on the recommended dose and mean body weight reported in the BALANCE trial (4.51 vials per year) using the submission's assumed AEMP for agalsidase alfa ($4,171.63).
[g] Same as for d with 100% compliance rate.

6.79 The estimated drug cost/patient/year would be $[redacted] based on the submission's proposed AEMP of $[redacted] per vial of pegunigalsidase alfa and assuming a mean body weight of 78.89 kg (based on the BALANCE trial) and 100% compliance.

Estimated PBS usage & financial implications

6.80 This submission was not considered by DUSC.

6.81 The submission used a mixed method approach to estimate the predicted use and cost of the requested PBS listing of pegunigalsidase alfa for the treatment of FD in patients with end-organ damage. In the absence of utilisation and cost data from the LSDP for agalsidase alfa and agalsidase beta, the submission calculated the number of patients eligible for treatment with pegunigalsidase alfa using an epidemiological approach and then applied a market share approach to estimate the uptake of pegunigalsidase alfa over a six-year period.

6.82 The key inputs used in the financial analysis are summarised in Table 13 .

Table 13 : Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population treated with ERTs			
Prevalence rate of FD	2.41 per 100,000	Prevalence rate used in the migalastat March 2024 PSD.	In June 2022, the LSDP EP advised that, based on recently available evidence, Fabry disease no longer meets the prevalence (1:50,000 threshold) criterion for the LSDP. The rate applied in the submission appears reasonable based on previous PBAC considerations for FD, although noting the actual prevalence rate in Australia remains uncertain.
Prevalence growth rate	8.4%	Based on the increase in prevalence reported in Chin and Fuller, 2022 between the period 1980-1996 (1 in 117,000) to 2009-2020 (1 in 14,000).	It is reasonable to assume a growth in prevalence; however, the proposed growth rate is high and uncertain. The growth rate was calculated using the reported prevalence from Chin and Fuller, 2022, from two periods of time. The gap between these periods is substantial and is likely not a true reflection of the year-on-year growth in prevalence. The growth rate is higher than the rate (6.9%) applied in the financial estimates of the migalastat March 2024 PBAC meeting consideration.
Proportion with symptoms of end-organ damage	30%	LSDP 2023 FD review	This is reasonable.
Proportion with amenable mutation	45%	Benjamin et al., 2017	This is reasonable in the absence of data on the proportion of FD patients with amenable mutation in Australia. The submission noted that this proportion fell within the range estimated by Hughes et al.,2017 (35-50%). The migalastat March 2024 PSD also appeared to apply the same proportion for amenable mutations to its financial estimates (Table 10, migalastat, PSD, March 2024 PBAC meeting with May 2024 addendum).
Proportion with non-amenable mutation	55%	100% minus the proportion of patients with amenable mutation (45%)	This approach was reasonable.
Migalastat market share for amenable mutations	50%	Based on assumed market share rates used in the migalastat March 2024 PSD.	This may be reasonable, although uncertain.
ERT market share for non-amenable mutations	100%	Sponsor assumption	This is reasonable given that there are no other treatments available for FD patients with non-amenable mutations available in Australia.
Treatment utilisation			
Uptake rate	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Sponsor assumption	This is uncertain. There is no data to support this assumption.
Costs			

Data	Value	Source	Comment
Proposed medicine (pegunigalsidase alfa)	$[redacted]	Requested weighted published DPMQ (submission assumed public/private split of 60%/40%)	The price applied in the financial estimates was based on the cost-minimised price against migalastat with a [redacted]% price premium. This was not reasonable.
Comparator medicines (agalsidase alfa and agalsidase beta)		Assumed	As these prices are unknown to the sponsor, they were assumed to be 50% above the price of migalastat.
MBS costs	$123.05	MBS item 13950	This MBS item is for the cost of IV administration (per infusion) for the administration of antineoplastic agents. The MBS item is not appropriate as it relates to administration of neoplastic agents only. It may be appropriate to apply MBS item 116 ($87.30) as the infusion would likely be overseen by a specialist in the consulting room or hospital. The submission did not estimate any change in utilisation to the MBS; however, there may be some impact to the MBS if the use of migalastat is displaced.

Source: Compiled during the evaluation using Table 4.1-1, p116 of the submission; Table 4.2-7, p124 of the submission; Table 4.5-2, p128 of the submission, Section 4 workbook; migalastat, PSD, March 2024 PBAC meeting with May 2024 addendum.
Abbreviations: ABS, Australian Bureau of Statistics; DPMQ, dispensed price for maximum quantity; ERT, enzyme replacement therapy; EP, expert panel; FD, Fabry disease; IV, intravenous; LSDP, Life Saving Drugs Program; MBS, Medicare Benefits Schedule; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document.

6.83 The estimated use and financial impact of listing pegunigalsidase alfa on the PBS based on the submission's assumed prices is shown in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of scripts dispensed[a]	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated financial implications of pegunigalsidase alfa						
Cost to PBS[b]	[redacted]3	[redacted]4	[redacted]4	[redacted]5	[redacted]6	[redacted]6
Estimated financial implications for agalsidase alfa and agalsidase beta						
Cost to LSDP	[redacted]7	[redacted]7	[redacted]7	[redacted]7	[redacted]7	[redacted]7
Net financial implications						
Net cost to health budget	[redacted]7	[redacted]7	[redacted]7	[redacted]7	[redacted]7	[redacted]7

Source: Compiled during the evaluation from Table 4.2-4, p122 of the submission; Table 4.2-9, p124 of the submission; Table 4.5-7, p132 of the submission; Table 4.5-8, p138 of the submission.
Abbreviations: LSDP, Life Saving Drugs Program; PBS; Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.
[a] Assuming 13.04 scripts per year as estimated by the submission.
[b] The net impact is proposed to be only to the PBS given that 100% PBS usage (i.e., 0% RPBS usage) is estimated.
The redacted values correspond to the following ranges:
[1] <500
[2] 500 to < 5,000
[3] $0 to < $10 million
[4] $10 million to < $20 million
[5] $20 million to < $30 million
[6] $30 million to < $40 million
[7] net cost saving

6.84 At year 6, the estimated number of patients was <500. The total cost to the PBS of listing pegunigalsidase alfa was estimated to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first six years of listing. The submission estimated that the overall net cost to the health budget of listing pegunigalsidase alfa is a saving of $0 to < $10 million in Year 1, to a saving of $0 to < $10 million in Year 6, resulting in a cumulative cost saving of $30 million to < $40 million in the first six years of PBS-listing. The net cost saving observed is largely driven by the estimated offsets due to displacement of current ERTs (agalsidase alfa and agalsidase beta) listed on the LSDP and the assumed higher price for these ERTs (50% above the price of migalastat).

6.85 These financial estimates are uncertain and should be interpreted with caution because:

- The price of pegunigalsidase alfa applied was based on the estimated annual cost of migalastat with a % price premium (Table 11). As discussed in paragraphs 6.58 and 6.63, there is no evidence to support the request for a price premium.
- The submission applied a baseline prevalence of 2.41 per 100,000 based on data presented in the migalastat March 2024 PSD. There is uncertainty in the prevalence that has been applied. The LSDP Expert Panel has determined, based on recently available evidence, that Fabry disease no longer meets the prevalence criterion for the LSDP.
- The prevalence growth rate (8.4%) applied in the submission is high compared to 6.9% that was considered in the migalastat March 2024 PBAC meeting consideration (paragraph 6.40, migalastat, PSD, March 2024 PBAC meeting with May 2024 addendum). When a 6.9% growth rate was applied, the net financial estimates across six years decreased by 7% from base case.
- The submission assumed that 0% of migalastat utilisation will be displaced if pegunigalsidase alfa is listed on the PBS. Migalastat has the administrative advantage over pegunigalsidase alfa (oral versus IV); therefore, it may be reasonable to assume that no use of migalastat would be displaced. There is no evidence, however, to suggest that there is a difference in effectiveness between the treatments, and while it is likely that more patients would opt for migalastat as it is an oral therapy, there may still be a small number of patients and/or clinicians who switch to pegunigalsidase alfa (for example patients who struggle with fasting two hours before and after taking migalastat or patients that experience IRRs).
- The submission assumed that -% of agalsidase alfa and agalsidase beta utilisation will be displaced by pegunigalsidase alfa if it is listed on the PBS (i.e., -% uptake rate across Years 1 to 6 assumed for pegunigalsidase alfa). The uptake rates and, ultimately, the market share of pegunigalsidase alfa with the other ERTs, is assumed and is uncertain. When this was decreased by 10%, the net financial estimates across six years decreased by 10% from the base case.

6.86 Both pegunigalsidase alfa and the existing ERTs (agalsidase alfa and agalsidase beta) require IV administration at the same frequency of once per fortnight. The submission has assumed that because these treatments utilise the same MBS item, the net impact to the MBS would be zero as the additional cost of administering pegunigalsidase alfa will be offset by the reduced IV administration costs associated with the reduction in utilisation of agalsidase alfa and agalsidase beta. This may be reasonable, however, given the uncertainty in the assumption that the use of migalastat will not be displaced if pegunigalsidase alfa is PBS-listed, the impact on the MBS if pegunigalsidase alfa is PBS-listed is uncertain. The magnitude of this impact is likely to be small relative to the cost of the medications.

6.87 The PSCR maintained the price requested for pegunigalsidase alfa is lower than the price of ERTs currently on the LSDP, and listing pegunigalsidase alfa at the price requested will result in a cost saving to Government.

6.88 The ESC note that the submission applied an arbitrary 50% premium to the cost of migalastat to estimate cost of agalsidase alfa and agalsidase beta on the LSDP.

6.89 The ESC considered that the uptake rate of pegunigalsidase alfa from other ERTs was assumed and uncertain. The pre-PBAC response stated that the uptake figures were based on estimates from the sponsor, which were informed by discussions with local clinicians and uptake rates internationally. The pre-PBAC response acknowledged the uptake rate was uncertain, but maintained that pegunigalsidase alfa would replace the higher-priced ERTs on the LSDP, resulting in a cost-savings regardless of uptake rate.

6.90 The ESC considered that the prevalence growth rate of 8.4% applied in the submission's financial estimates model was high and uncertain. The ESC advised that the submission had overestimated the number of patients and that the financial impact was therefore also overestimated. The pre-PBAC response acknowledged this, and stated that to address this uncertainty, sensitivity analyses varying the estimate by ±10% were provided.

6.91 The ESC advised that a prevalence growth rate of 6.9% (as applied to the financial estimates for the migalastat March 2024 PBAC consideration) would be appropriate. The ESC advised that data from the LSDP should be used to inform the financial estimates, however this data is held in-confidence by the Department. The pre-PBAC response stated that, using a scenario with a lower 6.9% growth rate resulted in a $20 million to < $30 million cost saving over 6 years, and a 7% reduction from the base case. The pre-PBAC response also acknowledged that this estimate was based on an assumed 50% price premium for ERTs compared to migalastat.

6.92 The PBAC agreed that a prevalence growth rate of 6.9% was appropriate for the financial estimates.

6.93 The pre-PBAC response maintained that listing pegunigalsidase alfa would provide clinical value and potential cost savings by replacing ERTs currently on the LSDP.

Quality Use of Medicines

6.94 The sponsor has proposed to provide a web-based patient support program to support home infusion for patients prescribed pegunigalsidase alfa, following its TGA registration. The option to enrol in a home infusion program may only be considered in patients tolerating their infusions well with no history of moderate or severe IRRs. The patient is required to have had at least six infusions of pegunigalsidase alfa in a hospital setting prior to consideration for the program and the decision to move to home infusion will be made after evaluation and recommendation by the treating physician. Home infusions must be conducted by a trained healthcare professional, under the direction of the treating physician. The sponsor will coordinate this program (through a third-party provider) and provide accredited nurses to deliver infusions.

6.95 The submission has estimated that four patients will initially enrol in the program in 2026, with up to 38 patients in 2030. The estimated number of patients from the submission that will enrol in the program is lower than the 40% of patients that underwent home infusion in the BALANCE trial. It is possible that the number of enrolments will be higher than anticipated based on this trial data.

6.96 The sponsor has also proposed to develop healthcare professional (HCP) and patient material in consultation with local experts and Fabry Australia that will be disseminated through company sponsored educational events and third-party sponsorships, including local congresses such as the Lysosomal Storage Disorder Summit. All activities will comply with the Medicines Australia Code of Conduct.

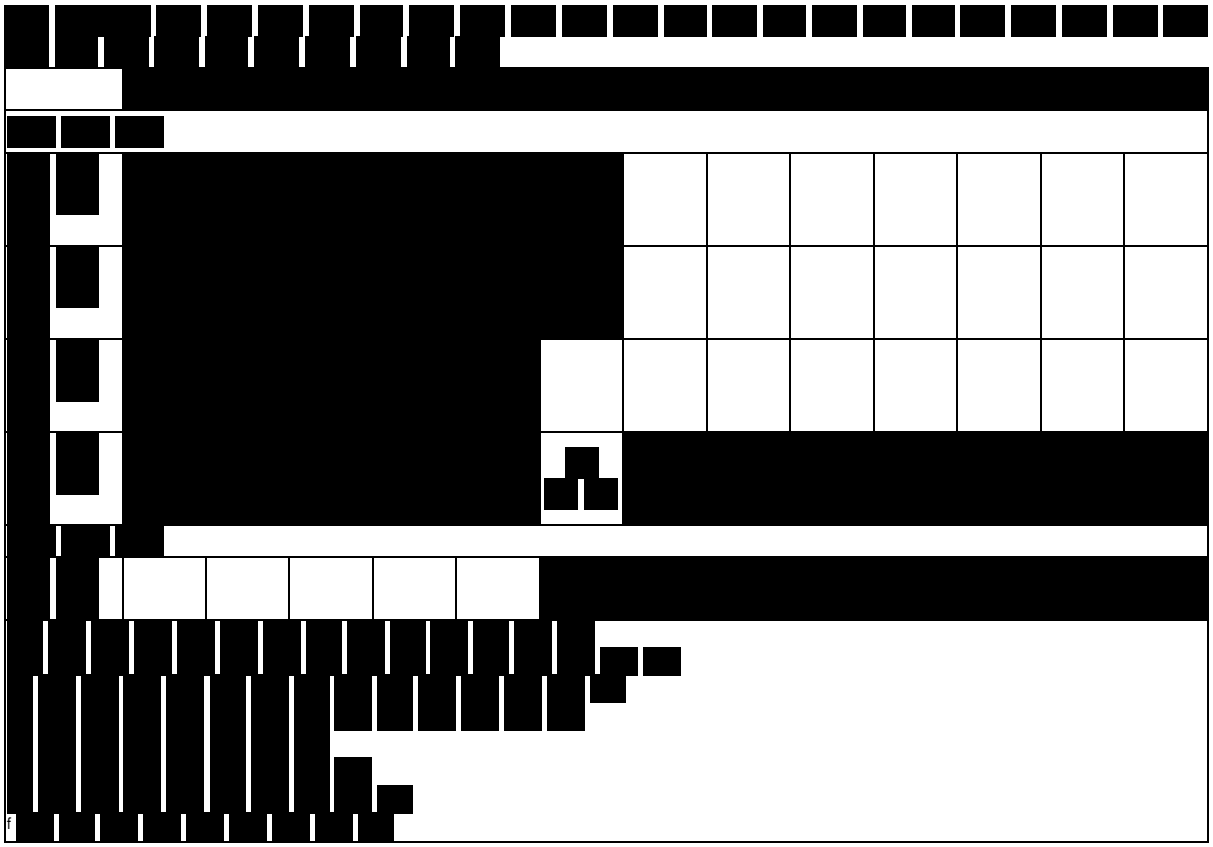
6.97 Local patient brochures for any patient commencing treatment with pegunigalsidase alfa will be developed and supplied to the treating physician by the sponsor. Materials will contain relevant links to the Consumer Medicines Information and the packaging will be as per the approved PI and TGA requirements.

Financial Management – Risk Sharing Arrangements

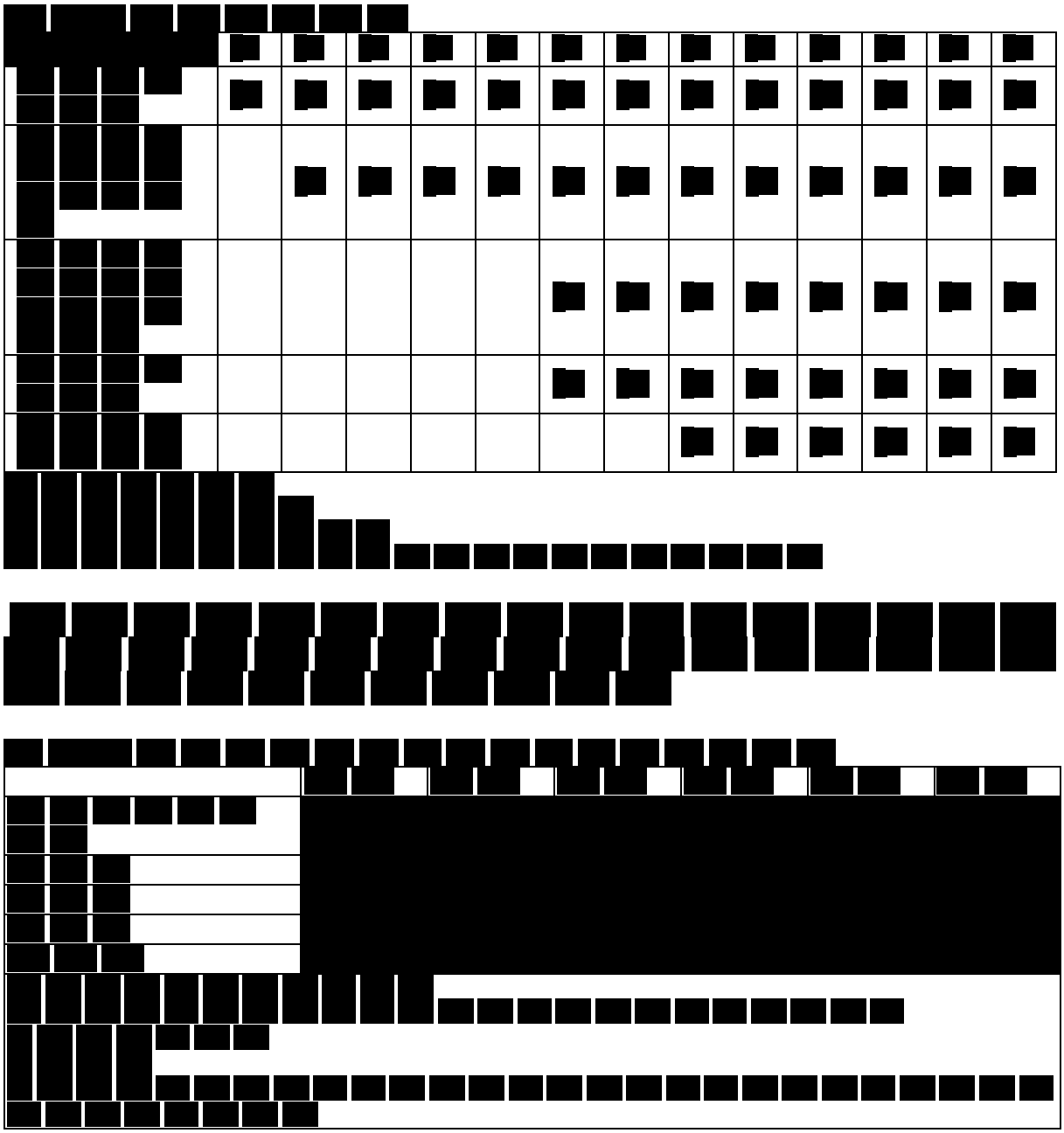
6.98 No risk-sharing arrangements (RSA) were proposed in the submission. The submission noted that migalastat has an RSA in place; however, the submission argued that it would not be appropriate for pegunigalsidase alfa to be included in that RSA given that it is only relevant for a proportion of FD patients (i.e., those with an amenable mutation).

Committee-In-Confidence information

[redacted]



[redacted]



End Committee-In-Confidence information

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of pegunigalsidase alfa for the treatment of Fabry Disease (FD) as an Authority Required (Written) listing for initial treatment and an

Authority Required (telephone/electronic) listing for continuing treatment, on the basis that it should be available only under Section 100 (Highly Specialised Drugs Program (Public and Private)). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of pegunigalsidase alfa would be acceptable if it were cost minimised to migalastat.

7.2 The PBAC noted that two other enzyme replacement therapies (ERTs) – agalsidase alfa and agalsidase beta – are currently available through the Life Saving Drugs Program (LSDP), and migalastat is the only medicine listed on the PBS for FD. The PBAC considered pegunigalsidase alfa provides an alternative therapy for FD.

7.3 The PBAC noted consumer comments received which described the challenges with living with FD, including difficulties in carrying out daily living activities (e.g. work, socialising), and the need for access to effective treatments. The PBAC further noted that having medications for FD available on the PBS would make them more accessible to patients.

7.4 The PBAC considered the claim that pegunigalsidase alfa has non-inferior efficacy compared to agalsidase beta was adequately supported. The PBAC considered there was a lack of clinical evidence to support the claim of non-inferior efficacy compared to agalsidase alfa, however it was reasonable to conclude that agalsidase alfa has similar efficacy to agalsidase beta, and therefore pegunigalsidase alfa.

7.5 The PBAC considered the claim of non-inferior comparative effectiveness compared to migalastat was supported by the data provided, with a high level of uncertainty. The PBAC noted the submission did not present an indirect treatment comparison or robust evidence, and the side-by-side comparison presented was difficult to interpret due to diversity in the patient populations of the studies.

7.6 The PBAC considered the claim of non-inferior safety compared to agalsidase alfa, agalsidase beta and migalastat, to be reasonable.

7.7 The PBAC considered that while the other ERTs would be appropriate clinical comparators, as they are not listed on the PBS, PBS-listed migalastat is an appropriate comparator. The PBAC noted that migalastat is listed on the PBS only for FD with an amenable mutation, which accounts for approximately half of the FD population.

7.8 The PBAC noted the submission requested a price that was a [redacted]% price premium over the annual cost of migalastat. However, the PBAC considered there was a lack of evidence demonstrating that pegunigalsidase alfa had superior efficacy, or a superior safety profile, compared to migalastat, and therefore a higher price than that of migalastat was not justified. The PBAC considered pegunigalsidase alfa to have non-inferior comparative efficacy and safety to migalastat, and recommended listing pegunigalsidase alfa on a cost-minimisation basis to migalastat. The PBAC recalled that migalastat was recommended with a cost per patient per year based on 12 packs per year of migalastat, consistent with the financial estimates provided for migalastat and the basis for the RSA (paragraph 7.7, 7.8 and 7.10, migalastat, PSD, March 2024 PBAC

meeting with May 2024 Addendum). The PBAC advised that the annual cost for pegunigalsidase alfa should not exceed the cost of 12 packs of migalastat per year.

7.9 The PBAC advised the equi-effective doses are pegunigalsidase alfa 78.9 mg every 2 weeks to migalastat 123 mg every other day.

7.10 The PBAC advised that the listing for pegunigalsidase alfa should align with the listing for migalastat where appropriate. The PBAC recommended:

- a Grandfather (Authority Required (Written)) listing for patients who are currently on a different enzyme replacement therapy through the LSDP and wishing to transition to pegunigalsidase alfa on the PBS. The PBAC recalled that it had previously advised in March 2024 that the Grandfather restriction for migalastat may need to be in place for longer than the standard timeframe of 12 months, depending on the transition of other treatments for FD onto the PBS. The PBAC advised the Grandfather restriction for pegunigalsidase alfa should also not be time limited.
- the maximum quantity in the listing be 1 x 10 mL vial, with prescribers able to request the number of vials required, based on the patient's weight, to allow for 4 weeks of treatment. Each treatment phase would allow up to 5 repeats.
- the listing be age-agnostic.
- removal of the requested clinical criterion 'Patient must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m^2', as the Product Information states that no dose adjustment is needed in patients with renal impairment.
- the clinical criterion relating to Fabry-related cardiac disease be aligned to the clinical criterion in the migalastat listing.
- inclusion of the clinical criterion 'The treatment must be the sole PBS-subsidised therapy for this condition' to prevent the concomitant use of FD therapies.
- a separate treatment phase allowing patients to switch from using pegunigalsidase alfa to migalastat and vice versa.

7.11 The PBAC recommended the following flow-on changes to the migalastat listing:

- Addition of the clinical criterion 'The treatment must be the sole PBS subsidised therapy for this condition' to prevent the concomitant use of FD therapies.
- A separate treatment phase allowing patients to switch from using migalastat to pegunigalsidase alfa and vice versa.
- Amend the 'antiepileptic' medications terminology to 'antiseizure' medications in the criterion 'Patient must have Fabry-related uncontrolled chronic pain despite the use of recommended doses of appropriate analgesia and **antiseizure** medications for peripheral neuropathy'.

7.12 The PBAC advised that pegunigalsidase alfa is suitable for prescribing by medical practitioners only, specifically physicians with expertise in the management of Fabry disease and is not suitable for prescribing by nurse practitioners.

7.13 The PBAC considered the financial estimates to be uncertain. The PBAC considered the number of patients with FD to be reasonable, and the prevalence growth rate of 6.9% to be appropriate. However, the PBAC considered that the estimated number of patients treated with pegunigalsidase alfa should be informed by LSDP data (noting that this data is held in-confidence by the Department). The PBAC considered the uptake rate of pegunigalsidase alfa to be highly uncertain, as it was based on the sponsor's estimates and it was unclear how many patients will switch from using alternative therapies to pegunigalsidase alfa. Listing pegunigalsidase alfa on the PBS may result in a higher uptake from ERTs on the LSDP as it will be easier for clinicians to prescribe compared to treatments on the LSDP. However, being a newer ERT and prescribers being less familiar with pegunigalsidase alfa compared to alternatives may lower uptake rates. The PBAC noted that patients switching from the LSDP to PBS treatment will lead to a net save to the health budget.

7.14 In light of the uncertainties of the financial estimates and usage, the PBAC considered it would be appropriate for there to be a risk sharing arrangement (RSA) for pegunigalsidase.

7.15 The PBAC advised that the financial estimates and RSA caps should be based on the estimated uptake rate from ERTs on the LSDP as proposed by the sponsor (% in Year 1, increasing to % in Year 6, see Table 13). The PBAC advised a % rebate for expenditure over the caps would be appropriate.

7.16 The PBAC requested a review of the utilisation of medicines for FD on the PBS be undertaken following 2 years of listing on the PBS.

7.17 The PBAC recommended that pegunigalsidase alfa should not be treated as interchangeable with any other drugs.

7.18 The PBAC recommended that the Early Supply Rule should not apply.

7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because pegunigalsidase alfa is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over migalastat, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.20 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
PEGUNIGALSIDASE ALFA						
pegunigalsidase alfa 20 mg/10 mL injection, 10 mL vial		NEW	1	1	5	Elfabrio
Concept ID	**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
	Prescriber type: ☒ Medical Practitioners					
	Benefit type: ☒ Authority Required (FULL assessment) in writing via OPA/post/HPOS upload)					
	Authority type: ☒ Complex Authority Required (CAR)					
	Prescribing rule level:					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
Restriction Summary [new1] / Treatment of Concept: [new1A]						
	Indication: Fabry disease					
	Treatment Phase: Initial treatment					
	Clinical criteria:					
	Patient must have at least one of: (i) documented deficiency of alpha-galactosidase enzyme activity in blood, (ii) presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity.					
	AND					
	Clinical criteria:					
	Patient must be male with Fabry-related renal disease confirmed by at least one of the following: (i) abnormal albuminuria of more than 20 mcg/min, as determined by 2 separate samples at least 24 hours apart, (ii) abnormal proteinuria of more than 150 mg/24 hours, (iii) albumin: creatinine ratio greater than upper limit of normal in 2 separate samples at least 24 hours apart, (iv) renal disease due to long-term accumulation of glycosphingolipids in the kidneys; OR					
	Patient must be female with Fabry-related renal disease confirmed by at least one of the following: (i) proteinuria of more than 300 mg/24 hours with clinical evidence of progression, (ii) renal disease due to long-term accumulation of glycosphingolipids in the kidneys; OR					
	Patient must have Fabry-related cardiac disease confirmed by at least one of the following: (i) left ventricular hypertrophy, as evidenced by cardiac magnetic resonance imaging (MRI) or echocardiogram data, in the absence of hypertension, (ii) significant life-threatening arrhythmia or conduction defect, (iii) late gadolinium enhancement or a low T1 on cardiac MRI; OR					
	Patient must have Fabry-related either: (i) ischaemic disease, (ii) cerebrovascular disease as shown on objective testing with no other cause or risk factors identified; OR					
	Patient must have Fabry-related uncontrolled chronic pain despite the use of recommended doses of appropriate analgesia and antiseizure medications for peripheral neuropathy; OR					
	Patient must have significant Fabry-related gastrointestinal symptoms despite the use of the recommended doses of appropriate pharmacological therapies.					

	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease.
	Prescribing Instructions: If hypertension is present in patients relying their eligibility on Fabry-related cardiac disease, the prescriber must treat it optimally for at least 6 months prior to submitting the first PBS authority application.
	Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports including the confirmed mutations must be documented in the patient's medical records.
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the proposed prescription(s); and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: At the time of authority application, prescribers must request the appropriate number of vials, based on the weight of the patient, to provide sufficient drug for 4 weeks of treatment at the dosage regimen specified in the approved Therapeutic Goods Administration (TGA) Product Information (PI).
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary [new2] / Treatment of Concept: [new2A]	
	Indication: Fabry disease
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated clinical improvement or stabilisation of condition, the details of which must be kept with the patient's record
	AND
	Clinical criteria:

	Patient must not have developed another life threatening/severe disease where long term prognosis is unlikely to be influenced by this drug.
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease.
	Prescribing Instructions: At the time of authority application, prescribers must request the appropriate number of vials, based on the weight of the patient, to provide sufficient drug for 4 weeks of treatment at the dosage regimen specified in the approved Therapeutic Goods Administration (TGA) Product Information (PI).
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Restriction Summary [new3] / Treatment of Concept: [new3A]	
	Indication: Fabry disease
	Treatment Phase: Grandfather arrangement (transition from LSDP-funded Fabry disease therapy)
	Clinical criteria:
	Patient must have previously received treatment with enzyme replacement therapy for this condition funded under the Australian Government's Life Saving Drugs Program (LSDP) prior to [PBS listing date].
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports including the confirmed mutations must be documented in the patient's medical records.
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include and must include: (1) details of the proposed prescription(s); and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: At the time of authority application, prescribers must request the appropriate number of vials, based on the weight of the patient, to provide sufficient drug for 4 weeks of treatment at the dosage regimen specified in the approved Therapeutic Goods Administration (TGA) Product Information (PI).

	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary [new4] / Treatment of Concept: [new4A]	
	Indication: Fabry disease
	Treatment Phase: Switching from PBS-subsidised migalastat
	Clinical criteria:
	Patient must have received prior treatment with PBS subsidised migalastat for this condition
	AND
	Clinical criteria:
	Patient must not have developed another life threatening/severe disease where long term prognosis is unlikely to be influenced by this drug
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
	Patient must not have failed to demonstrate clinical improvement or stabilisation of this condition with previous PBS-subsidised treatment with this drug.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease
	Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports including the confirmed mutations must be documented in the patient's medical records.
	Prescribing Instructions: At the time of authority application, prescribers must request the appropriate number of vials, based on the weight of the patient, to provide sufficient drug for 4 weeks of treatment at the dosage regimen specified in the approved Therapeutic Goods Administration (TGA) Product Information (PI).
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Flow on changes

8.2 Flow-on changes to the migalastat PBS listing for Fabry disease (FD):

1. Add a clinical criterion to the migalastat (14573B) restriction to prevent the concomitant use of FD therapies.

	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.

2. Add a new 'switching' treatment phase to the migalastat (14573B) restriction to allow patients to switch from pegunigalsidase alfa to migalastat and vice versa on the PBS.

Restriction Summary [new4] / Treatment of Concept: [new4A]	
	Indication: Fabry disease
	Treatment Phase: Switching from PBS-subsidised pegunigalsidase alfa
	Clinical criteria:
	Patient must have received prior treatment with PBS subsidised pegunigalsidase alfa for this condition
	AND
	Clinical criteria:
	Patient must not have developed another life threatening/severe disease where long term prognosis is unlikely to be influenced by this drug
	AND
	Clinical criteria:
	Patient must have a documented migalastat amenable galactosidase alpha (GLA) gene variant
	AND
	Clinical criteria:
	Patient must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
	Patient must not have failed to demonstrate clinical improvement or stabilisation of this condition with previous PBS-subsidised treatment with this drug
	Treatment criteria:
	Must be treated by a physician with expertise in the management of Fabry disease
	Population criteria:
	Patient must be at least 12 years of age
	Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports including the confirmed mutations must be documented in the patient's medical records.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

3. Amend the 'antiepileptic' medications terminology to 'antiseizure' medications in the criterion 'Patient must have Fabry-related uncontrolled chronic pain despite the use of recommended doses of appropriate analgesia and antiseizure medications for peripheral neuropathy'.

	Clinical criteria:
	Patient must have Fabry-related uncontrolled chronic pain despite the use of recommended doses of appropriate analgesia and ~~antiepileptic~~ *antiseizure* medications for peripheral neuropathy; OR

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The Sponsor welcomes the PBAC's recommendation of pegunigalsidase alfa for the treatment of Fabry Disease.