

An addendum has been included at the end of the Public Summary Document (PSD).

5.33 MIGALASTAT,

**Capsule containing migalastat hydrochloride 150 mg
Galafold[®],
Amicus Therapeutics Pty Ltd**

1 Purpose of submission

- 1.1 The Category 2 submission requested the PBAC reconsider its previous recommendation to list migalastat as a General Schedule Authority Required (Written) listing for the treatment of Fabry disease and to request an amendment to the restriction criteria to be consistent with international clinical guidelines for Fabry disease.

2 Background

Registration status

- 2.1 Migalastat was TGA registered on 11 August 2017 for the long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (alpha-galactosidase A (α -Gal A) deficiency) and who have an amenable mutation. The TGA registration was updated on 15 November 2022 to include adult and adolescent patients 12 years and older.

Previous PBAC consideration

- 2.2 The PBAC previously considered migalastat in March 2017, July 2017, November 2017 and December 2022. Subsequent to the November 2017 consideration, migalastat was included on the Life Savings Drug Program (LSDP). The December 2022 consideration was on the basis of a referral from the LSDP Expert Panel (EP) who advised that Fabry disease no longer met the requirements for inclusion on the LSDP. A summary of each consideration is provided in Table 1.

Table 1: Previous PBAC considerations of migalastat

	March 2017 (major submission)	July 2017 (minor submission)	November 2017 (minor submission)	December 2022 (referral from LSDP EP)
Clinical evidence	Migalastat vs ERT in treatment-experienced patients: ATTRACT study (n=52 patients with amenable mutations). Migalastat vs placebo in treatment-naïve patients: FACETS study (n=50 patients with amenable mutations).		Some additional longer term data for ATTRACT, FACETS was presented.	No new evidence presented. The LSDP EP 24 month review did not identify any additional clinical evidence for migalastat.
Clinical claim	Migalastat is non-inferior in terms of comparative effectiveness and safety over the primary comparator, ERT The PBAC considered that the outcomes of the trials did not provide confidence in the superior effectiveness of migalastat compared to placebo or equivalent effectiveness of migalastat compared to ERT. The PBAC considered.....it was reasonable to accept the claim of non-inferior comparative safety compared to ERT.			Unchanged
Economic evaluation				The PBAC considered 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.
Cost per patient per year	\$█ (requested by sponsor)	\$█ (requested by sponsor)		\$█ ¹
Financial estimates	10 to 21 treated patients per year	Unclear from minutes		40 to 62 treated patients per year
Outcome	Deferred pending the outcome of TGA consideration	The PBAC did not recommend the listing of migalastat for the treatment of Fabry disease. In making this decision, the PBAC was uncertain about the submission's clinical claim of non-inferior comparative effectiveness compared with ERT.	The PBAC did not recommend the listing of migalastat for the treatment of Fabry disease. In making this decision the PBAC considered that the submission's clinical claim of non-inferior comparative effectiveness compared with ERT remained uncertain and could not be supported.	The PBAC recommended the Authority Required listing of migalastat on the PBS for the treatment of Fabry disease in patients aged 16 years of age and older who have an amenable mutation.

Source: Table 1, migalastat PSD, December 2022 PBAC meeting

Abbreviations: EP = expert panel; ERT = enzyme replacement therapy, LSDP = live saving drugs program; PBAC = pharmaceutical benefits advisory committee; PBS = pharmaceutical benefits scheme; PSD = Public Summary Document

¹ Calculated as \$█ (current LSDP price)/28x365.25

2.3 At the December 2022 PBAC meeting, the PBAC recalled its previous consideration that the cost of migalastat should not be greater than the cost of the form of agalsidase which has the lowest cost to the Commonwealth, with a further significant price reduction reflective of the uncertainty around the claim of non-inferiority to

[enzyme replacement therapy] ERT. The PBAC noted the cost per patient for the ERTs is highly variable due to the use of weight-based dosing and that migalastat was more costly than the ERTs at the lower end of the range of likely patient weights. Therefore, the PBAC considered migalastat would be appropriate for PBS listing at a price that ensured it was less expensive than the lowest cost available ERT on the LSDP for Fabry disease for all patients aged 16 years of age and older, and that this could be achieved with a cost per patient per year no higher than the cost of ERT for a patient weighing 45 kg (Paragraph 5.6, migalastat Public Summary Document (PSD), December 2022 PBAC meeting).

LSDP EP consideration

- 2.4 The LSDP EP completed a review of Fabry disease in October 2020 and the EP evaluation overview was provided to the PBAC at the December 2022 meeting. Migalastat was not included in the protocol for the review as it had only recently become available on the LSDP at the time of protocol development.
- 2.5 The LSDP EP completed a 24-month review of the listing of migalastat on the LSDP and the overview of the review was provided to the PBAC at the December 2022 meeting. As part of this review, the EP discussed the sponsor's request to allow use of migalastat as a first line treatment (i.e., removal of the requirement for 12 months of ERT prior to accessing migalastat). The sponsor of migalastat provided a response to a draft version of the review and this was provided to the PBAC at the December 2022 meeting.
- 2.6 The LSDP EP further considered the sponsor's request to amend the criteria for migalastat at its June 2022 meeting. The minutes of the meeting were provided to the sponsor and the PBAC at the December 2022 meeting. The Fabry Australia Treatment Review White Paper referred to by the LSDP EP as part of its consideration is available on the Fabry Australia website¹. A version of this White Paper has recently been published as Nicholls 2024².

¹ <https://www.fabry.com.au/preventing-the-consequences/>

² Nicholls K et al (2024). Fabry-specific treatment in Australia: time to align eligibility criteria with international best practices. *Internal Medicine Journal*. <https://doi.org/10.1111/imj.16327>

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIGALASTAT					
Migalastat 123 mg capsules, 14	Published \$28,075.98 Effective \$	1	14	5	Galafold

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
Indication: Fabry disease
Treatment Phase: Initiation treatment
Clinical criteria:
Patient must have at least one of (i) documented specific deficiency of alpha- galactosidase enzyme activity in blood or white cells, (ii) presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity. AND Patient must have a documented migalastat amenable GLA gene variant with an eGFR of at least 30 mL/min/1.73 m ² . AND <ul style="list-style-type: none"> • Patient must be male, with non-classical Fabry disease, and have Fabry related renal disease confirmed by at least one of the following: (i) abnormal albumin (> 20µg/min), as determined by 2 separate samples at least 24 hours apart, (ii) abnormal protein excretion (>150mg/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 non-classical Fabry disease, have Fabry related renal disease confirmed by at least one of the following: (i) proteinuria >300mg/24 hours with clinical evidence of progression, (ii) renal disease due to long-term accumulation of glycosphingolipids in the kidneys. OR • Patient must have non-classical Fabry disease, and Fabry-related cardiac disease confirmed by at least one of the following: (i) Left ventricular hypertrophy, as evidenced by cardiac MRI or echocardiogram data, in the absence of hypertension, (ii) Significant life-threatening arrhythmia or conduction defect. OR • Patient must have non-classical Fabry disease, and have ischaemic vascular disease as shown on objective testing with no other cause or risk factors identified. OR • Patient must have non-classical Fabry disease and have uncontrolled chronic pain despite the use of maximum doses of appropriate analgesia and antiepileptic medications for peripheral neuropathy. OR • Patient must be male, with classical Fabry disease. OR • Patient must be female, with classical Fabry disease, and have evidence of injury to the kidney, heart or central nervous system that is attributable to Fabry disease. OR • Patient must be female, with classical Fabry disease, and have significant symptoms from Fabry disease that are affecting their quality of life
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:
If hypertension is present in patients with Fabry-related cardiac disease, the prescriber must treat it optimally for at least 6 months prior to submitting PBS application.

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Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
Indication: Fabry disease
Treatment Phase: Continuing treatment
Clinical criteria:
<p>Clinical criteria: Patient must have received prior PBS-subsidised treatment with this drug for this condition.</p> <p>AND Patient must have demonstrated clinical improvement or stabilisation of this condition.</p> <p>AND Patient must have not developed another life threatening or severe disease where long term prognosis is unlikely to be influenced by migalastat.</p> <p>AND The patient must have not developed another medical condition that might reasonably be expected to compromise a response to migalastat.</p>
Treatment criteria: Must be treated by a physician with expertise in the management of Fabry disease

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
Indication: Fabry disease
Treatment Phase: Grandfather treatment (transition from LSDP-funded migalastat)
Clinical criteria:
<p>Clinical criteria: Patient must have previously received this drug for this condition funded under the Australian Government's Life Saving Drugs Program (LSDP)</p> <p>AND Patient must have at least one of (i) documented specific deficiency of alpha- galactosidase enzyme activity in blood or white cells, (ii) presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity.</p> <p>AND Patient must have a documented migalastat amenable GLA gene variant</p> <p>AND Patient must have an eGFR of at least 30 mL/m².</p>
<p>Prescribing Instructions: If hypertension is present in patients with Fabry-related cardiac disease, the prescriber must treat it optimally for at least 6 months prior to submitting PBS application.</p> <p>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.</p>
Treatment criteria: Must be treated by a physician with expertise in the management of Fabry disease

- 3.1 The proposed effective price was █████% lower than the current LSDP price.
- 3.2 The PBAC previously noted that the LSDP EP was supportive of the removal of the clinical criteria from the LSDP criteria that patients must previously have had 12 months of ERT treatment or be intolerant to ERT prior to initiating migalastat and that the LSDP previously recommended the initial and continuing restriction criteria be brought into line with current International Clinical Guidelines for Fabry disease as

outlined in the Fabry Australia Treatment Review White Paper (Nicholls 2022). (paragraphs 3.2 and 3.3, migalastat PSD, December 2022 PBAC meeting).

- 3.3 The proposed restriction represented a change from the current LSDP eligibility, which does not currently differentiate between classical and non-classical (also referred to as late-onset) Fabry disease. The proposed definitions for diagnosis for classical and non-classical Fabry disease are presented in Figure 1.

Figure 1: Classical and non-classical Fabry disease phenotypes

Classical Male	Classical Female	Non-classical Male	Non-classical Female
<ul style="list-style-type: none"> • A likely pathogenic or pathogenic variant in the <i>GLA</i> gene • One or more of the following characteristic symptoms of Fabry disease: <ul style="list-style-type: none"> ○ Fabry neuropathic pain ○ Corneal verticillate ○ Angiokeratomas ○ Severely decreased or absent leucocyte alpha-Gal A enzyme activity ($\leq 5\%$ of the mean reference value*) 	<ul style="list-style-type: none"> • A likely pathogenic or pathogenic variant in the <i>GLA</i> gene • One or more of the following characteristic symptoms of Fabry disease: <ul style="list-style-type: none"> ○ Fabry neuropathic pain ○ Corneal verticillate ○ Angiokeratomas 	<ul style="list-style-type: none"> • A likely pathogenic or pathogenic variant in the <i>GLA</i> gene • Not fulfilling the criteria for classical male Fabry disease 	<ul style="list-style-type: none"> • A likely pathogenic or pathogenic variant in the <i>GLA</i> gene • Not fulfilling the criteria for classical female Fabry disease

* alpha-Gal A reference range: 2.0 to 6.9 nmol/h/mL [$\leq 5\% = \leq 1.0$ nmol/h/mL]; alpha-Gal A, alpha-galactosidase A; *GLA*, Galactosidase Alpha

Source: Table 3, p19 of the submission

- 3.4 The proposed criteria for initial treatment allow male patients with classical Fabry disease to initiate treatment without any symptoms. There were two issues with the proposed restriction:

- The threshold for determining classical Fabry disease in males was proposed to be $\leq 5\%$ of the mean reference value for α -Gal A enzyme activity but inappropriately this was not described in the proposed restriction. However, a threshold of $\leq 5\%$ was not universally accepted. For example, UpToDate³ suggested that ‘undetectable activity (<3 per cent) was sufficient to diagnose classic Fabry disease’ in males. Similarly, <3% was also the threshold used to classify classical Fabry disease in an expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease (Germain 2022)⁴. Michaud (2020)⁵ also used a threshold of <3% when aiming to summarize the clinical manifestations of Fabry disease and advice on how to diagnose Fabry disease. The ESC considered a threshold of 5% was reasonable and that this should be included in the restriction criteria.

³ Wallace E, (2023), Gene test interpretation: GLA (Fabry disease gene), UpToDate, accessed 15 November 2023

⁴ Germain D et al. (2022), An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease, *Molecular Genetics and Metabolism*, 137, pp48-61

⁵ Michaud et al. (2020) When and How to Diagnose Fabry Disease in Clinical Practice. *American Journal of the Medical Sciences*. 360(6), pp641-649

- There was little evidence to support the use of Fabry disease specific treatment (i.e. ERT or migalastat) in asymptomatic patients. According to the European Fabry Working Group consensus document (Biegstraaten 2015), which was referenced by Ortiz 2018 and further referenced by Nicholls 2022, while ERT may be considered in male patients aged 16 years or older with classical Fabry disease even if they have no symptoms or clinical signs of organ involvement, this was a Class IIb recommendation in which “usefulness/efficacy is less well established by evidence/opinion”. The Canadian Fabry Disease Treatment Guidelines⁶ also noted that data was lacking on the effects of treatment with disease specific therapy before there is detectable evidence of end organ involvement so treatment before end organ involvement could not be recommended, and instead regular monitoring for signs of Fabry related organ involvement should be conducted so disease specific therapy, if needed, can be initiated at an early phase in the disease. The ESC noted the Nicholls 2024 paper stated there is accumulating clinical outcomes data to support initiation of treatment in asymptomatic males with classical Fabry disease.
- 3.5 Given that the proposed criteria for diagnosis in classical male Fabry patients requires only a diagnosis based on genetic status and enzyme activity, it was possible that male patients may be diagnosed prior to 12 years of age. However, migalastat is not indicated for patients aged younger than 12 years and these patients would have to delay treatment until they meet the population criteria of being at least 12 years of age.
- 3.6 The proposed restriction for initial treatment also allows for female patients with a likely pathogenic or pathogenic variant in the GLA gene who also exhibit one (or more) Fabry related symptoms including Fabry neuropathic pain, corneal verticillate or angiokeratomas to initiate treatment with migalastat as a classical Fabry disease patient. However, Mauhin 2020⁷ reported that, among 104 Fabry disease patients in France, while the absence of acroparesthesia or cornea verticillata was sufficient to classify males as having the non-classical phenotype, the authors did not identify any criteria that significantly cluster female patients. Mauhin 2020 was unable to classify the 50 female patients in their sample as classical or non-classical. As such, it was unclear if the presence of corneal verticillate was an accurate marker for classical Fabry disease in female patients. In general, it appears that differentiating between classical and non-classical Fabry disease in females is more challenging than in males as they may exhibit residual enzyme activity, and as Michaud 2020 noted, “neuropathic pain, angiokeratomas, and/or cornea verticillata are major clinical

⁶ Sirrs S et al. (2018) Canadian Fabry Disease Treatment Guidelines 2018. Sherbrooke Quebec. Accessed 15 Nov 2023 via <https://www.garrod.ca/guidelines-and-resources>

⁷ Mauhin W et al (2022) Cornea verticillata and acroparesthesia efficiently discriminate clusters of severity in Fabry disease. PLoS One. 15(5):e0233460. doi: 10.1371/journal.pone.0233460.

characteristics for FD diagnosis in its classical form and may be absent in females with classical FD and with late-onset forms in both sexes”.

- 3.7 The proposed clinical criteria for initial treatment in non-classical Fabry patients were the same as the proposed clinical criteria for initial treatment considered at the December 2022 PBAC meeting and consistent with the current LSDP treatment criteria for Fabry disease. The submission referred to the symptoms included in the proposed clinical criteria as indicative of end organ damage. The PBAC considered the intent of the proposed restriction criteria was to identify patients with signs/ symptoms of major organ involvement or evidence of injury to major organs (described as ‘end organ involvement/injury’ herein).
- 3.8 The proposed restrictions allowed the use of migalastat as first line treatment in ERT naïve Fabry disease patients with end organ involvement/ injury whereas currently on the LSDP, patients must have been treated with ERT for 12 months before initiating migalastat. This was consistent with the PBAC’s previous considerations (paragraph 5.10, migalastat PSD, December 2022 PBAC meeting).
- 3.9 The proposed restriction to allow treatment of classical male patients when asymptomatic and classical female patients before they demonstrate organ involvement may be considered as ‘early treatment with migalastat’ as at least some of these patients would eventually become eligible under the organ involvement criteria due to disease progression.
- 3.10 The submission refers to the population of classical Fabry disease patients who would be eligible for early treatment with migalastat and ERT naïve patients with evidence of organ involvement/injury who are treated with migalastat as the extended population. This extended population formed the basis for the tiers in the proposed RSA. This is discussed further in paragraphs 6.46 and 6.47.
- 3.11 The PBAC previously raised concerns regarding the determination of amenability for migalastat using the Galafold Amenability Table (GAT). The LSDP EP review stated that GAT may identify patients with in vitro amenability who are not clinically amenable to migalastat, and suggested that patients have an early review of all clinically relevant information, at around 3 to 6 months. The pre-PBAC response claimed that the GAT will rule out patients who almost certainly would not respond to migalastat (paragraph 4.3, migalastat PSD, December 2022 PBAC meeting). The proposed number of repeats will allow initial treatment for up to 24 weeks, and the proposed continuation criteria require patients to have demonstrated clinical improvement or stabilisation of their condition.

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

4 Population and disease

- 4.1 Fabry disease is a rare, X-linked genetic disorder caused by a deficiency in the enzyme α -Gal A. Deficiency of α -Gal A results in accumulation in the body of

globotriaosylceramide (also known as GB3 or GL-3) and other related glycosphingolipids. This can cause long-term complications in organs throughout the body including the kidneys, heart and brain.

- 4.2 In general, males are more severely affected than females. Females with Fabry disease are heterozygous for the Fabry gene mutation and have a 50 per cent chance of passing the gene on to daughters or sons. Females have a variable disease course that ranges from asymptomatic disease to a severe phenotype resembling that seen in males. This phenotypic variation may be due in large part to random X-chromosome inactivation, by which some cells will have the X chromosome with the defective gene activated and others will have the X chromosome with the functioning gene activated. (UpToDate 2023⁸)
- 4.3 Treatment for Fabry disease in Australia is focused on correcting enzyme deficiencies through ERT or the use of migalastat. Migalastat acts directly on α -Gal A to reduce GB3/GL-3 accumulation as a “pharmacologic chaperone” and is administered to patients orally once every other day. ERT is administered via IV infusion once every fortnight. ERT can be used in patients of any age, and does not depend on amenability to a specific treatment.
- 4.4 The submission proposed that migalastat be available as first line treatment in patients aged 12 years and above who have an amenable mutation if they were:
- Male patients with classical Fabry disease, with or without any symptoms;
 - Female patients with classical Fabry disease if they have evidence of injury to the kidney, heart or central nervous system (CNS) that is attributable to Fabry disease or have significant symptoms from Fabry disease that are affecting their quality of life; and
 - Patients with non-classical Fabry disease and have organ involvement/injury.
- 4.5 Implicitly, the submission proposed that ERT will become second line therapy in patients aged 12 years or older with classical Fabry disease who have an amenable mutation, as these patients would be able to access migalastat, but not ERT until the disease has progressed such that they meet the LSDP treatment criteria. This was not consistent with the clinical guidelines summarised by the submission in which ERT and migalastat were both considered first line therapies across several guidelines, including Nicholls 2024.

5 Comparator

- 5.1 No comparator was explicitly nominated by the submission though a claim of non-inferior efficacy to ERTs was made. There is currently no PBS subsidised treatment for Fabry disease. ERT (with agalsidase alfa or agalsidase beta) on the LSDP was previously

⁸ Mauer M, et al. Fabry disease: Clinical features and diagnosis. UpToDate, accessed 10 January 2024.

nominated as the comparator at the March 2017 PBAC meeting, which was considered reasonable as ERTs were the treatment most likely replaced by migalastat (paragraph 7.2, migalastat PSD, March 2017 PBAC meeting).

- 5.2 However, LSDP subsidised ERT is not available for male patients with classical Fabry disease without any symptoms, or in female patients with classical Fabry disease with symptoms that do not meet the definition of end organ involvement/ injury. As such, in these patients, ERT would not be the appropriate comparator and instead watchful waiting until the patient meets the LSDP treatment criteria would be the most appropriate comparator. That is, in the proposed classical Fabry population, the comparator should be 'delayed treatment' (i.e. watchful waiting until LSDP treatment criteria were met) compared to the intervention of early treatment with migalastat.
- 5.3 Early treatment represents two different treatment regimens in the proposed restrictions:
- 'Asymptomatic early treatment', an earlier treatment at diagnosis for male classical Fabry disease patients (can be treated when asymptomatic); and
 - 'Symptomatic early treatment', a more delayed (but still earlier than current requirement for signs of organ involvement/injury) treatment initiation for female classical Fabry disease patients (must have one or more injury to the kidney, heart or CNS attributable to Fabry disease or if Fabry disease symptoms affect quality of life).

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease and how migalastat would be used in practice. The clinician emphasised that (i) the leading Fabry experts in Australia advocate changing the reimbursement criteria to reflect current clinical evidence; (ii) phenotypic stratification into classic and non-classic disease for treatment initiation will maximise benefit to patients; and (iii) timely treatment (before organ damage) is critical for the best outcomes, especially in classic patients. In response to the Committee's question, the clinician noted gastrointestinal symptoms are not a criteria on LSDP but are a very important physiological symptom for children and adolescents, in particular, and have significant effect on daily activities. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (47), health care professionals (7) and organisations (7) via the Consumer Comments facility on the PBS website.

- 6.3 Several health care professionals emphasised the effectiveness of migalastat in treating Fabry disease, noting that if diagnosed and treated early, migalastat may prevent disease progression and organ involvement, and lead to increased quality of life and life expectancy. They noted (i) the irreversible nature of the disease; (ii) the need for quick and effective treatment via the PBS; and (iii) the lack of medical evidence to support a requirement of 12 months therapy with ERT prior to migalastat. The health care professionals also commented on the benefits of oral treatment (versus infusion), but noted the education required relating to administration outside of food consumption and the need for regular clinician oversight.
- 6.4 The comments from individuals to support migalastat listing were received from Fabry disease patients (both current migalastat patients and those who would like to access the medicine) and family members/carers. In addition to the comments provided by health care professionals, individual comments focused on ability to travel and access in rural/regional areas.
- 6.5 Comments regarding migalastat for Fabry disease were received from the following organisations:
- Fabry Australia
 - Genetic Alliance Australia
 - National Fabry Disease Foundation in the United States
 - Australian Pompe Association
 - Rare Voices
 - Genomics Research Centre Diagnostic Clinic
 - Human Genetics Society of Australasia.

In addition to the comments raised by health care professionals and individuals, the PBAC noted the organisations' advice that certainty is required around continuity of access for those patients who have been accessing migalastat on the LSDP, and that listing on the PBS would provide the best mechanism for preventing significant organ damage and subsequent health effects.

- 6.6 The PBAC noted that the advice from health care professionals, individuals and organisations was supportive of the evidence provided in the submission.

Clinical studies

- 6.7 The submission presented the following clinical evidence:
- Results from one head-to-head trial (ATTRACT) comparing migalastat to ERT (intention to treat (ITT), n=60; modified ITT (mITT) amenable, n=52) in treatment-experienced patients, and one head-to-head trial (FACETS) comparing migalastat to placebo (ITT, n=67; mITT amenable, n=50) in treatment-naïve patients. The PBAC has considered the results from these trials previously at the March 2017 PBAC meeting;

- Extended long-term outcomes (up to 8.6 years) in patients enrolled in ATTRACT and FACETS (Bichet 2021 and Hughes 2023) to support the durability of treatment; and
- A summary of retrospective studies (Hughes 2021, Parini 2020, Feriozzi 2020, Germain 2015, Germain 2013) comparing treatment with ERT in Fabry disease patients at different ages and at different stages of disease to support the use of migalastat as early disease-specific therapy in patients with classical Fabry disease. The evaluation considered that given that the patients in these studies were not treated with migalastat there were significant applicability issues.

6.8 Details of the included trials presented in the submission are provided in Table 2.

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ATTRACT NCT01218659	Hughes D, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomise phase III ATTRACT study	Journal of Medical Genetics; 2017; 54(4): 288-296
FACETS NCT00925301	Germain, D et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat.	New England Journal of Medicine, 2016, 375(6), 545-555

Source: Constructed during the evaluation

6.9 Additionally, details of the extended long-term studies and retrospective studies used to support the submission are provided in Table 3.

Table 3: Extended long-term studies and retrospective studies presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Bichet 2021	Bichet D et al. Long-term follow-up of renal function in patients treated with migalastat for Fabry disease.	Molecular genetics and metabolism reports, 2021, 28, 100786
Hughes 2023	Hughes D et al. Long-term multisystemic efficacy of migalastat on Fabry-associated clinical events, including renal, cardiac and cerebrovascular outcomes.	Journal of medical genetics, 2023, 60(7), 722–731.
Hughes 2021	Hughes D et al. FOS Study Group. Prompt agalsidase alfa therapy initiation is associated with improved renal and cardiovascular outcomes in a Fabry Outcome Survey analysis.	Drug design, development and therapy, 2021;15: 3561–72.
Parini 2020	Parini R et al. Analysis of Renal and Cardiac Outcomes in Male Participants in the Fabry Outcome Survey Starting Agalsidase Alfa Enzyme Replacement Therapy Before and After 18 Years of Age.	Drug design, development and therapy, 2020, 14, 2149–2158.
Feriozzi 2020	Feriozzi S et al. Effects of baseline left ventricular hypertrophy and decreased renal function on cardiovascular and renal outcomes in patients with Fabry disease treated with agalsidase alfa: a Fabry Outcome Survey study.	Clinical Therapeutics. 2020;42(12):2321–30
Germain 2015	Germain D et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease.	Journal of Medical Genetics 2015, 52(5), 353–358.
Germain 2013	Germain D et al. Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: Data from the Fabry Registry.	Genetics in Medicine 2013, 15(12), 958–965
Warnock 2012	Warnock D et al. Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation	Nephrology Dialysis transplantation 2012, 27(3), 1042-1049
Hopkin 2023	Hopkins R et al. Clinical outcomes among young patients with Fabry disease who initiated agalsidase beta treatment before 30 years of age: An analysis from the Fabry Registry	Molecular genetics and metabolism 2023; 138(2), 106967

Source: Constructed during the evaluation

6.10 The key features of the direct randomised trials and the extended long-term studies and retrospective studies are summarised in Table 4 and Table 5, respectively.

Table 4: Key features of the comparative evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome
Migalastat vs. ERT					
ATTRACT	<ul style="list-style-type: none"> ITT, N = 60 mITT amenable, N = 52 	R, OL, MC 18 months	High	Treatment-experienced patients with Fabry disease and an amenable mutation, age 16-74 years	Annualised change in eGFR
Migalastat vs. placebo					
FACETS	<ul style="list-style-type: none"> ITT, N = 67 mITT amenable, N = 50 	R, DB, MC 6 months	High	Treatment-naïve patients with Fabry disease and an amenable mutation, age 16-74 years	Patients (%) with > 50% reduction in kidney interstitial capillaries GL3 inclusions

Source: Table 2, migalastat public summary document, March 2017 PBAC meeting

Abbreviations: DB = double blind; eGFR = estimated glomerular filtration rate; ITT = intention to treat; MC = multi-centre; mITT = modified intention to treat; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised.

Table 5 Key features of the extended long-term studies and retrospective studies

Long term migalastat					
Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome
Bichet 2021	78	OL, post hoc	High ^a	ERT-naïve (n=36 [63.9% female]; mean age 45 years) and ERT-experienced (n=42 [57.2% female]; mean age 50 years) population (aged 16-74 years) with Fabry disease and amenable GLA variants who received migalastat 123 mg every other day for ≥2 years during FACETS and ATTRACT trials plus the open label extension studies (AT1001-041 [NCT01458119] and AT1001-042 [NCT02194985]).	eGFRCKD-EPI (renal function) (as annualised rate of change) analysed by treatment status, sex, and phenotype.
Hughes 2023	97	OL, post hoc	High ^a	ERT-naïve (n=48 [62.5% female]; mean age 43.1 years) and ERT-experienced (n=49 [61.2% female]; mean age 49.5 years) population (aged 16-74 years) with Fabry disease and amenable GLA variants who had received migalastat treatment during FACETS and ATTRACT trials plus the open label extension studies (AT1001-041 [NCT01458119] and AT1001-042 [NCT02194985]).	Incidence of FACEs (as a composite outcome and separately for renal, cardiac and cerebrovascular events) analysed by sex, age, phenotype, and prior treatment status.
ERT observational retrospective studies					
Hughes 2021	Male 1130 Female 921	OL, Retro	High ^b	Patients enrolled in FOS who had been treated with agalsidase alfa	Probability of cardiovascular and renal events
Parini 2020	Male: 560	OL, Retro	High ^b	Male patients enrolled in FOS, stratified by age of ERT initiation ≤18 years of age (cohort 1; child), >18 and ≤30 years of age (cohort 2; young adult), and >30 years of age (cohort 3; adult).	Mean annual rates of change in eGFR, proteinuria, and LVMI
Feriozzi 2020	Male: 269 Female: 291	OL, Retro	High ^b	Patients enrolled in FOS who had been treated with agalsidase alfa during adulthood (age ≥18 years) who had not experienced dialysis or renal transplant prior to initiation of agalsidase alfa	Cardiovascular events and markers of disease progression: myocardial infarction, LVH, heart failure, arrhythmia, conduction abnormality, and cardiac surgery.
Germain 2015	Male: 50 Female: 2	OL, Retro	High ^b	Patients with classical Fabry disease who were enrolled in a phase 3 randomized trial of agalsidase alfa versus placebo ^c	Any clinical events, mean slopes for change in eGFR, LPWT and IVST.
Germain 2013	Treated male: 115 Untreated male: 48	OL, Retro	High ^b	Longitudinal Fabry registry patients treated with agalsidase beta and untreated, grouped into quartiles based on left ventricular mass slopes	Change in left ventricular mass per year
Warnock 2012	Male:151 Female: 62	OL, Retro	High ^b	Fabry Registry who received agalsidase beta at an average dose of 1 mg/kg/2 weeks for at least 2 years.	Mean eGFR slope, renal disease progression
Hopkins 2023 ^d	Male: 524 Female: 261	OL, Retro	High ^b	Fabry Registry patients with GLA variant predicted to be associated with classical Fabry disease or unclassified variants who initiated agalsidase beta between 5-30 years of age	eGFR slopes, self reported symptoms

Source: Table 10, p 29 of the submission

Abbreviations: eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; FACE = Fabry-associated clinical events; FOS = Fabry Outcome Survey; IVST = interventricular septum thickness; LPWT = left ventricular posterior wall thickness; LVH = left ventricular hypertrophy; LVMI = left ventricular mass indexed to height; OL = Open label, Retro = retrospective

^a Considered high risk of bias due to being open label and the *post hoc* nature of study as well as lack of a comparator arm, with comparisons being made against cohorts from other studies and includes substantial confounding.

^b Considered high risk of bias due open label nature of study, the lack of a comparator (except for Germain 2013) and retrospective nature of allocation of subgroups for comparisons. Further, the intervention being considered (ERT) was not migalastat and the PBAC has not accepted that ERT and migalastat are non-inferior therefore has potential applicability issues.

^c Eng CM et al. (2001) Safety and efficacy of recombinant human alphagalactosidase A—replacement therapy in Fabry's disease. *New England Journal of Medicine*;345:9–16

^d Incorrectly referenced as Hopkin 2016 in submission

Comparative effectiveness

- 6.11 The PBAC previously considered the results from ATTRACT and FACETS. At the December 2022 PBAC meeting, the PBAC recalled that it had previously not accepted the claim of non-inferior comparative effectiveness of migalastat compared to ERT in either treatment naïve or treatment experienced patients and noted there was no additional clinical evidence available, and the claim remained uncertain (paragraph 4.4, migalastat PSD, December 2022 PBAC meeting). No new comparative evidence was presented.
- 6.12 The submission also included longer term follow up of patients treated with migalastat from ATTRACT and FACETS. Bichet 2021 reported longer term renal function in 78 patients treated with migalastat for two or more years who were originally enrolled in ATTRACT and FACETS in a *post hoc* analysis, with a median (range) migalastat treatment duration of 7.0 (2.0–8.6) years and 5.1 (2.1–7.2) years for ERT naïve and ERT experienced patients, respectively. The results from Bichet 2021 as well as published annualised eGFR rates from a natural history study in Fabry disease patients (as reported in Schiffmann 2009⁹), ERT (as reported in Rombach 2013¹⁰ and Madsen 2019¹¹) and a healthy Japanese population (Baba 2015¹²), which were all referenced by Bichet 2021 as a comparison, are summarised in Table 6.

⁹Schiffmann R et al. (2009) Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy, *Nephrology Dialysis Transplant* 24: 2102–2111.

¹⁰Rombach S et al. (2013) Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain, *Orphanet Journal of Rare Disease* 8:47

¹¹Madsen C et al. (2019) Age-related renal function decline in Fabry disease patients on enzyme replacement therapy: a longitudinal cohort study, *Nephrology Dialysis Transplant* 34 1525–1533.,

¹² Baba M et al. (2015) Longitudinal study of the decline in renal function in healthy subjects, *PLoS One* 10, e0129036.

Table 6: Summary of changes in renal outcomes in patients treated with migalastat for two or more years in Bichet 2021 and in reference published studies.

	N	Baseline eGFR _{CKD-EPI} (mL/min/1.73m ²)		Annualised rate of change eGFR _{CKD-EPI} (mL/min/1.73m ²)	
		Mean (SD)	Median (range)	Mean (SD)	Median (range)
ERT naïve (median duration of migalastat treatment 7.0 years (range 2.0-8.6))					
Overall	36	91.4 (22.4)	92.0 (41.4-125.6)	-1.6 (3.1)	-1.1 (-2.6, -0.6)
Male	13	NR	NR	-1.8 (2.7)	-1.0 (-3.8, -0.8)
Female	23	NR	NR	-1.4 (3.3)	-1.1 (-1.7, -0.6)
Classical	10	86.4 (27.5)	94.8 (41.4-119.0)	-1.7 (3.0)	-0.9 (-4.0, 0.1)
Other	26	93.3 (20.4)	92.0 (44.6-125.6)	-1.5 (3.2)	-1.1 (-2.3, -0.7)
ERT experienced (median duration of migalastat treatment 5.1 years (range 2.1-7.2))					
Overall	42	89.2 (19.9)	88.9 (51.4-131.3)	-1.6 (3.6)	-1.3 (-2.2, -0.5)
Male	18	NR	NR	-2.6 (4.8)	-1.4 (-2.6, -0.7)
Female	24	NR	NR	-0.8 (2.1)	-1.1 (-2.1, -0.4)
Multiorgan involvement males ^a	15	NR	NR	-2.5 (5.1)	-1.3 (-2.6, -0.4)
Other	27	NR	NR	-1.1 (2.3)	-1.3 (-2.2, 0.5)
Published comparator groups cited by Bichet 2021					
Schiffmann 2009 (untreated Fabry disease patients, median follow up 5.6 years)					
Male baseline eGFR ≥60 mL/min/1.73m ²	189	NR	NR	-3.0 (SEM =0.1)	NR
Female baseline eGFR ≥60 mL/min/1.73m ²	129	NR	NR	-0.9 (SEM = 0.9)	NR
Male baseline eGFR ≥60 mL/min/1.73m ²	28	NR	NR	-6.8 (SEM = 1.5)	NR
Female baseline eGFR ≥60 mL/min/1.73m ²	13	NR	NR	-2.1 (SEM = 1.6)	NR
Rombach 2013 (US ERT treated Fabry disease patients, median follow up 5.5 years (range 0.51-10))					
Males	30	88.5 ± 40.6	NR	-3.4 (SE = 0.2)	NR
Females	27	86.6 ± 31.3	NR	-0.8 (SE = 0.3)	NR
Madsen 2019 (Danish ERT treated Fabry patients with ≥3 mGFR values, median 7 years (range 1-13))					
Males	20	121 ± 6	NR	-1.8 ± 0.5	NR
Females	32	98 ± 5	NR	-0.01 ± 0.4	NR
Baba 2015 (Healthy Japanese cohort who attended medical check up, mean interval for first and last check up 4.19±4.25 years in men and 4.35±2.47 years in women)					
Overall	45586	NR	NR	-1.07 (0.43)	
Males	21703	NR	NR	-1.03 (0.40)	
Females	23883	NR	NR	-1.11(0.44)	

Source: Constructed during evaluation using information from Table 1, Table 2 and Table 4 Bichet 2021, Table 3 Schiffman 2009, Table 2 and p3-4 Rombach 2013, p1529 Madsen 2019, Table 2 and p6-7 Baba 2015.

Abbreviations: eGFR_{CKD-EPI} = estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT = enzyme replacement therapy; mGFR = measured glomerular filtration rate; NR = not reported; SE = standard error; SEM = standard error of the mean

^a Baseline white blood cell α-Gal A activity in ERT-experienced patients was confounded by ERT and the same classic phenotype definition could not be applied. Instead, male patients with multiorgan involvement were compared with males without multiorgan involvement and females (specified above as "others").

- 6.13 The results of Bichet 2021 showed that the mean annualised rate of change in eGFR of patients treated with migalastat for two or more years ranged between -0.8 to -2.6 ml/min/1.73m². The standard deviation around the mean annualised eGFR changes in Bichet 2021 were generally large relative to the point estimates, reflective of the small sample size.
- 6.14 The submission claimed that Bichet 2021 concluded that the rate of renal decline observed in patients who received two or more years of migalastat were similar to or lower than ERT treated patients, lower than untreated historical cohorts and were comparable to the normal rate of decline in age. However, these were all single arm observational studies and any comparison across study results would be highly confounded and should be interpreted with caution. Notably, not all the results were consistent. For example, there were substantial differences in the point estimate for eGFR declines in Madsen 2019 compared to Rombach 2013 even though both included ERT treated patients, and the eGFR decline in healthy Japanese women in Baba 2015 (-1.11) was numerically worse than untreated females with Fabry disease with baseline eGFR ≥ 60 mL/min/1.73m² in Schiffmann 2009 (-0.9), as well as ERT experienced females treated with migalastat in Bichet 2021 (-0.8) and females treated with ERT in both Rombach 2013 (-0.8) and Madsen 2019 (-0.01). Overall, Bichet 2021 should not be relied upon as a source of comparative effectiveness.
- 6.15 The submission also reported results from Hughes 2023, who reported the incidence of Fabry-associated clinical events (FACE) and death due to FACE in 97 patients (48 ERT naïve and 49 ERT experienced) who were enrolled in ATTRACT and FACETS (and the extension studies) and treated with migalastat for up to 8.6 years (median 5.1 years, range 0.1-8.6). FACE were defined as:
- renal events, which included doubling of serum creatinine levels from the start of baseline (where levels remained double or greater between two consecutive values) or end-stage renal disease requiring long-term dialysis or transplantation;
 - cardiac events, which included myocardial infarction; new symptomatic arrhythmia requiring medication, direct current cardioversion or an interventional procedure (e.g. ablation, pacemaker or defibrillator implantation); unstable angina defined by national practice guidelines and accompanied by electrocardiographic changes; congestive heart failure requiring hospitalisation; any major cardiac medical procedure (e.g. valve replacement, stent implantation, transplant or persistent atrial fibrillation); and
 - cerebrovascular events, including stroke or transient ischaemic attack as documented by a physician.
- 6.16 Hughes 2023 reported an overall incidence of FACE of 48.3 per 1000 patient-years in patients treated with migalastat long term. The majority of ERT naïve (37/48, 77.1%) and ERT experienced (43/49, 87.8%) patients treated with migalastat did not experience any FACE, and overall, 17/97 (17.5%) of patients experienced 22 FACE

while on migalastat. A summary of the incidence of FACE per 1000 patient years in Hughes 2023 is presented in Table 7.

Table 7: FACE incidence (per 1000 patient years) in Hughes 2023

Per 1000 patient years	N	Total FACE	Renal	Cardiac	Cerebrovascular
Overall	97	48.3	4.4	30.7	13.2
Male	37	NR	11.5	40.2	17.2
Female	60	NR	0	24.9	10.7
Age ≤40 years	31	NR	0	0	8.8
Age >40 years	66	NR	5.8	40.9	14.6
ERT Naïve	48	48.6	4.1	32.4	12.3
Classical male	14	61.5	15.4	15.4	30.8
Others	34	44	0	38.5	5.5
ERT experienced	49	47.9	4.8	28.7	14.4
Male, multiorgan involvement	16	68.6	13.7	41.2	13.7
Other	33	36.8	0	22.1	14.7

Source: Figure 1, Hughes 2023

Abbreviations: ERT = enzyme replacement therapy, FACE = Fabry associated clinical event

- 6.17 Hughes 2023 also presented side by side comparisons of 49 patients who were treated with migalastat with 15 patients who continued treatment with ERT over 18 months. Following 18 months of treatment, in the overall migalastat population versus the continued ERT population, incidence rates were 60.6 vs 326.6 per 1000 person- years, respectively. Hughes 2023 subsequently claimed that migalastat was associated with a lower incidence of FACEs versus continued ERT.
- 6.18 While Hughes 2023 claimed that migalastat treated patients were older and ‘more clinically affected’ it was unclear how this was assessed. Though the baseline mean eGFR in the migalastat-treated patient group was lower (mean = 88.96 mL/min/1.73m², SD = 20.39) than in ERT-treated patients (mean = 95.81 mL/min/1.73m², SD = 21.04), the difference in age of migalastat treated patients (median 54.0 years) and ERT treated patients (median 48.0 years) would partially explain the difference in baseline eGFR and not necessarily reflect that migalastat treated patients were ‘more clinically affected’. Moreover, the time since Fabry diagnosis was substantially longer in ERT treated patients (mean 16.93 years, SD = 13.56 and median 10.0 years, range 6-27) than in the migalastat treated patients (mean 12.45 years, SD = 11.93 and median 6.0 years, range 5-18). Overall, this comparison should be interpreted with caution due to potential confounders as well as small patient numbers.
- 6.19 Hughes 2023 also presented side by side comparisons of their results against other published studies. The authors noted that cross study comparisons should only be made with caution due to disparate patient populations and procedures, but concluded that the incidence of FACEs with migalastat treatment appears to be comparable to that observed in similar datasets of ERTs. As noted by Hughes 2023, these comparisons are likely to be highly confounded and therefore should not be relied upon and no clear conclusion could be drawn. Further, the definition of FACE in each study also differed, making cross study comparisons even more uncertain.

- 6.20 The submission also presented a range of retrospective observational studies in patients who were treated with ERT and enrolled in either the Fabry registry or the Fabry outcome survey. These studies were used to support the use of migalastat as early disease-specific therapy in patients with classical Fabry disease.
- 6.21 The following issues should be considered when interpreting the results of included retrospective observational studies:
- All studies included patients treated with ERT and may not be applicable to migalastat. Additionally, except for Germain 2013 and Hopkin 2023, the studies did not consider only patients with classical Fabry disease for whom the early treatment restriction was sought;
 - The studies all used registry data and as such, there were often significant imbalances in baseline characteristics which confounded results, to an unknown and variable degree;
 - All studies reported a multitude of outcomes and analyses in a range of subgroups and comparisons, without any statistical planning for multiplicity. As such, the use of a 5% threshold for statistical significance (most studies reported 95% confidence intervals) would bias towards finding statistically significant differences in at least some of the comparisons;
 - None of the studies reported any outcomes in patients who were treated while asymptomatic;
 - In studies which considered the time delay from symptom onset or diagnosis to treatment, the time delay required to demonstrate a difference was usually a difference which was in excess of 10 years. For example, even though delayed treatment in Hughes 2021 was defined as ERT initiation ≥ 24 months from symptom onset and prompt treatment was defined as < 24 months from symptom onset, the actual mean time between symptom onset and treatment initiation was 1.0 years for prompt treatment and 20.4 years for delayed treatment. Therefore, Hughes 2021 did not actually compare treatment delays of < 24 months and ≥ 24 months but rather 1 year after symptom onset and 20 years after symptom onset. Studies which reported differences between long and short delays in treatment often reported no (or very minor) differences in consecutive decades of delay. For example, in Germain 2013, while a baseline age of ≥ 40 years was associated with left-ventricular hypertrophy progression compared with men younger than 30 years, there was no statistically significant difference when considering 30 to < 40 years and ≥ 40 years; and
 - Not all studies were in agreement in terms of the correlation with baseline differences and outcomes (see paragraph 6.22).
- 6.22 A summary of the included retrospective observational studies is as follows:

- A lower renal involvement (measured by a low urine protein-to creatinine ratio or low sclerotic glomeruli) at baseline of treatment initiation was correlated with a slower decline in renal function over time compared to patients with high renal involvement at baseline (Germain 2015 and Hopkin 2023).
- Similarly, less advanced (or no) left ventricular hypertrophy at ERT treatment initiation was correlated with slower growth of left ventricular muscle compared to patients with more advanced left ventricular hypertrophy at baseline (Feriozzi 2020).
- A shorter time between symptom onset and ERT initiation was correlated to better patient outcomes (Hughes 2021 and Warnock 2012). In Warnock 2012, male patients who had >24 years delay from Fabry symptom onset to first ERT infusion were more likely to have worse renal progression than those who had ≤24 years delay (OR 19, 95% CI 2–184, p=0.0098). However this was not statistically significantly different in women (OR = 0.31, 95% CI 0.047-2.041) based on results from 62 patients.
- Conflicting information as to whether baseline eGFR was correlated with better outcomes. Feriozzi 2020 reported that the subgroup with a low eGFR at baseline (n = 433) had a significantly higher risk for a cardiovascular event (HR =1.33; 95% CI, 1.04 1.70; P = 0.021) or a renal event (HR = 5.88; 95% CI, 2.73-12.68; P < 0.001) compared with patients with a normal eGFR at baseline (n= 60). However, Hopkin 2023 reported that in 13 patients with low renal involvement and baseline eGFR >135 mL/min/1.73m², the rate of eGFR decline (males: -2.95 mL/min/1.73 m²/year (95% CI -6.01, 0.12) and females: -3.20 mL/min/1.73 m²/year (95% CI -9.71, 3.32)) was numerically worse than the decline in the high renal involvement male cohort (n=23) (eGFR slope =-2.39 mL/min/1.73 m²/year).
- Conflicting information as to whether age at initiation of ERT was correlated with outcomes. For example, Parini 2020 and Germain 2013 both reported that an older age at baseline was correlated with worse outcomes. However in Hopkin 2023 the change in z-scores for left ventricular posterior wall thickness was not any different between younger or older patients at ERT initiation. In Hughes 2021, after accounting for sex, time from symptom onset or diagnosis and history of events, age at ERT initiation (in increments of 10 year increases) did not have any significant impact on risk of renal events, though it was marginally significant (HR = 1.01, 95% CI 1.01-1.02, P<0.001 when considering time from symptom onset; HR = 1.01, 95% CI 1.01-1.02, P<0.001 when considering time from diagnosis) for cardiovascular events with an extremely small effect.
- Conflicting information as to whether a longer delay from diagnosis to treatment was correlated with worse outcomes. In Warnock 2012, time to diagnosis to first infusion of ERT was not statistically significant once time to symptom onset was included in the regression, with patients who had a delay longer than 2.6 years (the median in the sample) from diagnosis to first infusion being numerically less likely

to have renal disease progression (men: OR = 0.62, 95%CI 0.11, 3.54; women: OR = 0.85, 95% CI 0.42, 1.71) though the difference did not appear to be statistically significant. However, in Hughes 2021, prompt treatment (<24 months from diagnosis, n=1006) from time of diagnosis significantly reduced the probability of cardiovascular events (HR=0.83; p=0.003) compared to delayed treatment (≥24 months from diagnosis, n = 1202). Univariate analysis showed that the probability of renal events was significantly lower in the prompt group (p=0.018); however, this finding was attenuated in the multivariate Cox regression analysis.

- 6.23 Overall, there was no evidence presented to support early treatment with migalastat. If evidence related to ERT is considered relevant to migalastat, the quality of evidence for supporting early treatment in classical Fabry patients was poor.

Comparative harms

- 6.24 No new safety information was provided in the submission. The PBAC previously considered the claim of non-inferior comparative safety of migalastat compared to ERT was reasonable (paragraph 5.5, migalastat PSD, December 2022 PBAC meeting).

Benefits/harms

- 6.25 A benefits and harms table has not been presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.26 The submission described migalastat as non-inferior in terms of effectiveness compared to ERT. The evaluation considered this claim was not adequately supported. The key issues were:
- No new comparative evidence was provided in the submission to support the claim of non-inferiority. The clinical claim was based on two head-to-head trials (ATTRACT and FACETS). However, both studies have been previously considered by the PBAC and the Committee previously found the available evidence for migalastat insufficient to support a claim of non-inferior effectiveness compared to ERT;
 - In the longer-term follow-up of patients treated with migalastat in ATTRACT and FACETS, Bichet 2021 claimed that in patients who received two or more years of migalastat, the rate of renal decline was similar to or lower than ERT treated patients, lower than untreated historical cohorts and were comparable to the normal rate of decline in age as reported in other studies. However, these were all single arm observational studies and any comparison across study results would be highly confounded and should be interpreted with caution. Migalastat treated (n=49) and ERT treated patients (n=15) who were compared in Hughes 2023 had substantial differences in time since Fabry diagnosis, which may have confounded results. Further, no formal statistical testing, minimally clinically important differences or non-inferiority margins were proposed to allow any sort of objective assessment of non-inferiority;

- No evidence for early treatment with migalastat in classical Fabry patients was presented and as such no conclusion could be drawn regarding the efficacy of migalastat in early treatment of Fabry disease in classical Fabry patients. While observational studies for ERT were presented to support early treatment in Fabry disease, the quality of evidence was poor. Results were not consistent across studies and the studies were highly confounded due to differences in baseline characteristics of patients and lack of multiplicity adjustments. The Pre-Sub-Committee Response (PSCR) noted that it is unlikely that RCT evidence comparing early versus late treatment will ever be available due to the rare and variable nature of the disease.
- 6.27 The submission described migalastat as non-inferior in terms of safety compared to ERT. The PBAC noted this claim has previously been accepted (paragraph 5.5, migalastat PSD, December 2022 PBAC meeting).
- 6.28 The PBAC considered the claim that migalastat is non-inferior in terms of effectiveness compared to ERT remained uncertain.

Economic analysis

- 6.29 No economic analysis was presented in the submission.
- 6.30 The PBAC previously considered that migalastat would be appropriate for PBS listing at a price that ensured it was less expensive than the lowest cost available ERT on the LSDP for Fabry disease for all patients aged 16 years of age and older, and that this could be achieved with a cost per patient per year no higher than the cost of ERT for a patient weighing 45 kg (paragraph 5.6, migalastat PSD, December 2022 PBAC meeting). The submission claimed that they were informally advised that a price reduction of approximately |% compared to the current annual cost of \$| (\$|/28 days x 365.25 days) would be required to secure a PBS listing consistent with the PBAC recommendation. The PSCR stated that to achieve this level of price reduction, a pragmatic broadening of the eligibility criteria has been proposed for migalastat to align with the available clinical evidence, international best practice in the management of Fabry disease as well as the opinions of Australian experts. The PSCR stated that this, combined with the risk sharing arrangement proposed, will result in clinical best practice and the level of saving per patient aligned to that which was communicated to the sponsor.
- 6.31 The submission proposed a ■■■% price reduction from the current LSDP list price, but claimed that with the proposed RSA, a |% price reduction will be achieved if the Tier 2 cap was reached with the proposed restriction. This is discussed further in paragraphs 6.46 and 6.47 below. The submission claimed that this would “cost-effectively allow for the proposed expansion of the population eligible for migalastat”.
- 6.32 The ESC considered it was unlikely the PBAC’s previous decision on the cost effectiveness of migalastat (as described in paragraph 6.30) would extend to the extended population of early treatment in patients with classical Fabry disease. As

such, the ESC noted the cost effectiveness of the proposed early treatment in classical Fabry patients should be considered unknown.

- 6.33 The pre-PBAC response stated that most patients with classical Fabry disease will progress to end organ damage and end up receiving targeted therapies by a mean age of 41 years (LSDP Technical Assessment, 2015). The response stated allowing early treatment with migalastat should substantially slow disease progression, resulting in savings to the healthcare system and improved quality of life.

Drug cost/patient/year

Table 8: Drug cost per patient for proposed drug (using ex-manufacturer prices)

	Economics (cost estimates)	Financial estimates
Mean dose	123 mg capsule, one capsule every second day	
Cost per patient/year	\$ ^a	\$ ^b

Source: Calculated during evaluation

^a Estimated using proposed AEMP of \$ [redacted] for 14 tablets and assuming 365.25 days.

^b Estimated using proposed AEMP of \$ [redacted] for 14 tablets and assuming 12 packs per year

- 6.34 The difference between the estimated cost per patient year in the trial and in the economics presented in the submission compared to the financial estimates was due to differences in the number of packs assumed. The economics estimates assumed 365.25 days per year and each pack (of 14 capsules) lasting 28 days, with an annual usage of 13.04 packs per year, whereas the financial estimates assumed 12 packs per year.

Estimated PBS usage & financial implications

- 6.35 This submission was not considered by DUSC.
- 6.36 The submission took a mixed approach to estimate the financial impact of listing migalastat:
- A market share approach (using the sponsor’s internal sale figures) was used to estimate the number of patients with evidence of organ involvement/injury who would be treated with migalastat as they would have if migalastat remained on the LSDP; and
 - A mixed market share and epidemiological approach was used to estimate (i) the number of additional patients with end organ involvement/ injury treated due to removal of requirement to have had 12 months of ERT prior to migalastat initiation as well as (ii) early treatment with migalastat in classical Fabry disease patients who meet the proposed restriction.
- 6.37 The key inputs for the financial estimates are presented in Table 9.

Table 9: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Number of patients with end organ involvement/injury to be treated with migalastat (as for current LSDP listing)	<p>█████² in year 1 increasing to █████² in year 6.</p> <p>Estimated based on linear extrapolation of monthly sales of migalastat on the LSDP, which the submission claims had increased from 29 units in January 2021 to 48 units in July 2023. An increase of 0.4107 patients per month was estimated.</p>	<p>The ESC noted █████² patients were treated on the LSDP in 2021/ 2022 and █████² in 2022/2023 and considered that an increase in the number of patients with organ involvement/injury of █████² to █████² per year (as estimated by the submission) was likely to be reasonable.</p>
Estimated total number of Australian Fabry disease patients	<p>█████¹ in year 1 increasing to █████¹ in year 6.</p> <p>Estimated by dividing number of Fabry disease patients currently treated under LSDP by estimated uptake of disease specific treatment (85%) and proportion of patients with end organ involvement/injury (30%).</p>	<p>Incidence rate estimated (between 1 per 4,886-5,524 live births) in the submission, substantially higher than reported in Chin 2022 (1 per 14,000 live births), indicating the number of Fabry patients is likely overestimated. May be associated with number of Fabry disease patients currently treated on LSDP being overestimated, as the submission assumes that the cost for ERT is equivalent to migalastat, even though ERT is dosed by weight and as such the expenditure to patient ratio will be different to that of migalastat.</p>
Proposed uptake rate of migalastat for early treatment in classical Fabry disease patients	<p>85% in classical Fabry patients, an assumption based on current uptake of disease specific treatment on the LSDP</p> <p>65.2% in proposed classical Fabry population who will receive early treatment will be treated with migalastat, based on assumption that migalastat had a total market share of 29.4% among all patients and 45% of all patients had amenable mutation (i.e. $29.4\% \div 45\% = 65.2\%$)</p>	<p>Unclear if uptake rate in classical patients (with lesser symptoms) would be the same as patients currently treated on the LSDP who have organ involvement/injury and may be overestimated. Further, given that ERT is not subsidised for early treatment in classical Fabry patients, the uptake of migalastat in this patient group would be substantially higher than 65.2% and should be 100%.</p> <p>Applying both rates was likely double counting and led to an underestimate in the number of patients who will use migalastat under the proposed restriction. However, the uptake rate in classical Fabry patients for early treatment may be overestimated and the overall impact was uncertain.</p>
Proportion of ERT naïve patients with end organ involvement/injury electing first line migalastat	<p>50% of ERT naïve patients with amenable mutation who have symptoms of end organ involvement/ injury would use migalastat (after removal of requirement to have 12 months of ERT)</p>	<p>The submission assumed that among patients who have an amenable mutation and treated with disease specific therapy on the LSDP, migalastat has a 65.2% market share.</p>

Parameter	Value applied and source	Comment
Proportion with amenable mutation	45% based on assumptions made in March 2017 submission of migalastat	Possible that amenable mutation in classic Fabry disease differs to the whole Fabry population. Nowak 2020 ¹³ reported that in a cohort of 170 adult Fabry disease patients in Switzerland, 84/170 (48%) had amenable mutations. Of patients with the classic phenotype, 43/129 (33%) had amenable mutations, compared to 41/41 (100%) in the late-onset phenotype. However, it was unclear if this would be applicable to the Australian population.
Proportion classical Fabry disease	Proportion of classical Male: 28.5% Proportion of classical Female: 29.9% Based on proportions reported in Arends 2017, a retrospective study of 499 adult Fabry patients in Germany, the United Kingdom, and The Netherlands	Arends 2017 was not conducted in an Australian population so may have uncertain applicability. Chin 2022 noted that the compositions of ancestries can affect incidence and prevalence and comparing Australia to other countries was difficult. As noted in paragraph 3.6, the diagnosis of females with classical Fabry disease may be challenging, and the prevalence may differ depending on the population and clinicians involved.
Proportion classical Fabry patients eligible for migalastat	Proportion of classical Male eligible: 100% Proportion of classical Female eligible: 75% Assumption made by submission	Proportion of classical females eligible was uncertain.
Number of migalastat scripts per year	12 scripts (each script lasts 28 days)	

Source: constructed during evaluation using information from p36-42 of the submission and BudgetImpact_migalastat.xlsx

Abbreviations: ABS = Australian Bureau of Statistics; ERT = enzyme replacement therapy; IV = intravenous; LSDP = life saving drugs program; PSD = public summary document

The redacted values correspond to the following ranges:

¹ 500 < 5,000

² < 500

6.38 The submission's financial estimates had several issues (beyond uncertainties in the assumptions of inputs) that may have led to inaccurate estimates:

- The submission assumed that the expenditure to patient ratio for ERT was the same as migalastat in the estimate of number of Fabry disease patients currently treated on the LSDP. However, as the cost of ERT was weight dependent this was not a valid assumption and the estimated number of Fabry disease patients was likely to be inaccurate and overestimated. This could be observed when comparing the incidence rate estimated by the submission (roughly one new case every 5,000 live births) being substantially higher than the incidence reported in Chin 2022 in Australia between 2009-2020 (one new case every 14,000 live births);
- The submission may have underestimated the uptake rate of early treatment with migalastat in classical Fabry disease patients, as both a 'proportion electing treatment' (85%) as well as an 'uptake of migalastat' rate (65.2%) was applied. Uptake of migalastat will be 100% in patients who elect early treatment as ERT is

¹³ Nowak A. et al. (2020) Fabry disease genotype, phenotype, and migalastat amenability: Insights from a national cohort. Journal of Inherited Metabolic Disease. Vol 43 Issue 2. pp326-333.

not indicated for early treatment in classical Fabry disease patients. This may have underestimated the number of classical Fabry disease patients who would be treated with early treatment under the proposed restriction.

- The submission estimated the number of Fabry disease patients who would receive early treatment as the difference between the estimated number of patients who would be eligible for and would elect early treatment (i.e. meet symptom/diagnosis criteria and have amenable mutation) with the number of patients with an amenable mutation who are already treated on the LSDP. While the submission appropriately accounted for the number of patients with amenable mutations who may have end organ involvement/ injury who were already assumed to be treated with migalastat from the cohort of classical Fabry disease patients who may be eligible for early treatment with migalastat, inappropriately no consideration of patients with amenable mutations and end organ involvement/ injury who may be treated with ERT was made. This may have led to an overestimate of the number of patients treated with early treatment under the proposed restriction.
- The submission's calculations implicitly assumed that all patients treated with ERT or migalastat on the LSDP were classical Fabry patients. If this assumption was violated (i.e. there is a proportion of late-onset Fabry patients treated on the LSDP) then the number of patients who will receive early treatment may be underestimated as the offsets for the number of classical Fabry patients already treated on the LSDP may be overestimated;
- The submission did not account for and remove ERT naïve patients with end organ involvement/ injury electing disease specific treatment from their estimation of patients who may be eligible for early treatment. This may have slightly overestimated the number of patients who may be eligible for early treatment. However, given the relatively small number of ERT naïve patients with end organ involvement/ injury electing disease specific treatment (eight per year) this may not have had a large impact on the total estimates; and
- It is possible that patients who are diagnosed may be too young to initiate on migalastat, which has a population criterion that the patient must be at least 12 years of age. These patients would not be able to start migalastat early treatment at diagnosis and would instead need to wait until they turn 12 years of age.

6.39 The number of patients who will be treated with migalastat as presented by the submission is summarised in Table 10. The financial impact to the PBS associated with the listing of migalastat for the proposed indication is summarised in Table 11.

6.40 The submission claimed that the increase in prevalence (from 2.41 per 100,000 to 3.36 per 100,000) calculated was around 6.9% per year, which was comparable to the increase in prevalence reported in Chin 2022 who reported a Fabry disease 'prevalence' of 1 in 117,000 between 1980-1996 and 1 in 14,000 in 2009-2020 which translated to an 8.4% increase per year. The definition of 'prevalence' in Chin 2022 and the definition of prevalence calculated in the submission were not the same. In

Chin 2022, ‘prevalence’ was calculated by dividing the total number of postnatal and prenatal diagnoses (median age of diagnosis at 44.6 years) during the study period by the number of live births during the study period, with ‘incidence’ estimated using the same approach with the exception of prenatal diagnoses. As such, ‘prevalence’ in Chin 2022 was actually an alternative method of estimating incidence, differing only in the type of diagnoses considered. Comparatively, prevalence in the submission (and more commonly used in the literature) refers to the number of cases divided by the total population at a given point in time. Instead, a comparison of the incidence rate in the submission with the incidence rate of Chin 2022 may be more appropriate.

Table 10: Submission’s estimates of number of patients using migalastat

	2024	2025	2026	2027	2028	2029
Migalastat use on PBS in patients with organ involvement/injury	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total number of Fabry disease patients in Australia	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated prevalence (per 100,000)	2.41	2.61	2.81	3.00	3.18	3.36
New Fabry disease cases ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated incidence (1 per X live births) ^b	█ ³	█ ²	█ ²	█ ³	█ ³	█ ³
Classical males	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Classical females	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Eligible classical males ^c	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Eligible classical females ^d	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total eligible for migalastat early treatment	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total classical patients electing early treatment ^e	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Projected migalastat uptake for early treatment in classical patients ^f	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of additional classical Fabry patients who will be treated with migalastat as early treatment ^g	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
New Fabry disease cases with end organ involvement/ injury, amenable mutation and will elect treatment	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Additional ERT naïve patients with end organ involvement/ injury treated with migalastat if requirement for 12 months of ERT is removed ^h	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total patients treated with migalastat	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹

Source: Table 12, p37, Table 14, p38, Table 15, p39, Table 16, p40, Table 17, p41 and Table 18, p42 of submission.

Abbreviation: LSDP = life saving drugs program

^a Number of Fabry disease patients in current year minus number of Fabry disease patients in previous year

^b Estimated using number of new cases divided by births (age 0 population) in ABS Population Projections, Australia – medium series.

^c Estimate 45% of all classical males will have amenable mutation, and 100% will be eligible

^d Estimate 45% of all classical females will have amenable mutation, and 75% will be eligible

^e Assumed 85% will elect treatment, based on LSDP EP estimates in the end organ involvement/ injury e population

^f Submission assumes that only 65.2% of the classical patients who elect early treatment will actually use migalastat

^g The number of patients treated with migalastat under current LSDP was removed from the projected migalastat uptake for early treatment in classical patients

^h Assumed 50% of newly diagnosed Fabry disease patients who would be eligible for treatment under the current LSDP listing for migalastat will be treated with migalastat. This population was also included as an offset to LSDP costs by the submission.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

Table 11: Submission’s estimates of financial impact of listing migalastat

	2024	2025	2026	2027	2028	2029
Migalastat use on PBS in patients with end organ involvement/ injury	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Additional ERT naïve patients with end organ involvement/ injury treated with migalastat if requirement for 12 months of ERT is removed	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of additional classical Fabry patients who will be treated with migalastat as early treatment	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total patients treated with migalastat	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of migalastat scripts ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net cost to PBS ^b	█ ³	█ ³	█ ³	█ ³	█ ³	█ ⁴
Cost offsets from LSDP						
Substituted patients now using migalastat on PBS	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Substituted patients using ERT on LSDP	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total substituted LSDP costs ^c	█ ⁵	█ ⁵	█ ³	█ ³	█ ³	█ ³

^a █ scripts per patient assumed

^b \$█ per script assumed, with a copayment of \$17.48 per script based on what appears to be nusinersen usage

^c Assumed \$█ per patient per year

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$10 million to < \$20 million

⁴ \$20 million to < \$30 million

⁵ \$0 to < \$10 million

- 6.41 The total cost to the PBS of listing migalastat was estimated to be \$20 million to < \$30 million in Year 6, and a total of \$100 million to < \$200 million in in the first six years of listing. The submission stated that this would be accompanied by a saving to the LSDP of \$10 million to < \$20 million in Year 6, and a total saving of \$\$60 million to < \$70 million in the first six years of listing.
- 6.42 The number of additional ERT naïve patients with organ involvement/injury treated with migalastat if requirement for 12 months of ERT is removed from the migalastat listing (four patients per year) was double that considered by the PBAC previously (Table 3, migalastat PSD, December 2022 PBAC meeting).
- 6.43 Overall, the ESC considered there was a high degree of uncertainty in the financial estimates given the issues with the submission’s financial estimates as outlined in

paragraph 6.38. Additionally, there was further uncertainty in the financial estimates due to uncertainties with regards to the key inputs used (as described in Table 9).

- 6.44 The ESC considered there was reasonable certainty regarding the number of patients with evidence of organ involvement/injury that would use migalastat on the PBS.
- 6.45 The pre-PBAC response noted the complexity of the analysis is partly driven by the need to estimate migalastat and ERT use on the LSDP based on migalastat sales data, expenditure caps and Department of Health and Aged Care notifications. However, this would be simplified if actual LSDP patient data were available and using the LSDP patient data both lowers the complexity and increases the certainty of the financial estimates.

Financial Management – Risk Sharing Arrangements

- 6.46 The submission proposed an RSA with two tiers. The first tier is based on uptake in the current LSDP population, plus the ERT-naïve population recommended by the PBAC in the December 2022 Migalastat PSD i.e. all patients with evidence of organ involvement/injury. The second tier is based on projected uptake in the proposed expanded classical population i.e. early treatment with migalastat. The submission proposed a rebate of |% for expenditure above the first tier, and |% rebate above the second tier.
- 6.47 The submission stated that if migalastat uptake remains at current LSDP levels (including a first line listing for migalastat), the Commonwealth government will save |% on migalastat expenditure. If migalastat uptake increases as a result of expanding the restriction, Commonwealth expenditure will increase but at an increasingly reduced net price per patient, with an approximately |% reduction per migalastat script at projected uptake assuming the Tier 2 cap was reached. The submission stated this predicted |% reduction in the net price is aligned with the price reduction requested by PBAC in December 2022 and would be a ‘cost-effective’ way of updating the criteria to access. However, the December 2022 decision relates only to usage in the population with organ involvement/injury and did not necessarily extend to early treatment in classical Fabry disease, which may not be cost effective at the same price.
- 6.48 Under the proposed RSA, total PBS expenditure on migalastat would be capped at \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6. A summary of the expenditure caps under the proposed RSA for migalastat on the PBS is provided in Table 12.

Table 12: Expenditure caps proposed by the submission

	2024	2025	2026	2027	2028	2029
Patients with organ involvement (Tier 1)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Early treatment in classical Fabry patients (Between Tier 1 and Tier 2)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total estimated patients treated with migalastat (Tier 2)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net cost to PBS without RSA	█ ³	█ ³	█ ³	█ ³	█ ³	█ ⁴
Cost to PBS with RSA						
Tier 1 ^a	█ ⁵	█ ⁵	█ ⁵	█ ³	█ ³	█ ³
Between Tier 1 and 2 ^b	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Tier 2 (maximum PBS expenditure)	█ ⁵	█ ³	█ ³	█ ³	█ ³	█ ³
Cost per script assuming Tier 2 cap reached	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
% reduction of cost per script assuming Tier 2 cap reached ^c	█ ⁵ %	█ ⁵ %	█ ⁵ %	█ ⁵ %	█ ⁵ %	█ ⁵ %

Source: Table 19, p43 and Table 20, p45 of the submission

Abbreviations: PBS = pharmaceutical benefit scheme; RSA = risk sharing arrangement

^a Number of patients with organ involvement multiplied by 12 scripts per patient per year at \$█ per script (DPMQ of \$█ minus \$17.48 copayment)

^b Number of classical Fabry disease patients treated with early treatment multiplied by 12 scripts per patient per year at \$█ per script (DPMQ of \$█ minus \$17.48 copayment, with a █% rebate applied)

^c Compared to current LSDP price of \$█ EMP per script

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$10 million to < \$20 million

⁴ \$20 million to < \$30 million

⁵ \$0 to < \$10 million

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of migalastat for the treatment of Fabry disease 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 recommended in December 2022 but considered that, on balance, noting the high clinical need for ongoing access to funded treatments for Fabry disease, 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. The PBAC considered the estimated number of patients with Fabry disease who had evidence of organ involvement/injury was likely to be reasonable.

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 Fabry disease without evidence of organ involvement/injury.

- 7.2 The PBAC noted the strong consumer support for adding migalastat to the PBS and the importance of continuity of access. The PBAC reiterated the importance of patients with Fabry disease having ongoing access to effective therapies.
- 7.3 The PBAC considered the restriction criteria should identify patients with Fabry disease and (i) signs/ symptoms suggesting major organ involvement or (ii) evidence of injury to major organs. The PBAC considered it would be appropriate for patients with cerebrovascular disease and severe gastrointestinal symptoms to be eligible for treatment with migalastat. The PBAC advised the following amendments to the restriction criteria recommended in December 2022 would be appropriate:
- Amend the population criterion 'Patient must be at least 16 years of age' to 'Patient must be at least 12 years of age'.
 - Amend the clinical criterion 'Patient must have at least one of (i) documented ~~specific~~ deficiency of alpha- galactosidase enzyme activity in blood ~~or white~~ cells, (ii) presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity' with deletions as per strikethrough.
 - Add the clinical criterion 'Patient must have significant Fabry-related gastrointestinal symptoms despite the use of the recommended doses of appropriate pharmacological therapies'.
 - Amend the clinical criterion 'Patient must have ischaemic vascular disease as shown on objective testing with no other cause or risk factors identified' to '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'.
- 7.4 The PBAC considered it was appropriate for the grandfathering restriction criteria to allow patients currently receiving LSDP-funded migalastat or enzyme replacement therapy (ERT) to transition to PBS-subsidised migalastat. The PBAC noted patients currently on LSDP-funded ERT transitioning to migalastat would need to (i) have an amendable mutation (ii) be over 12 years of age and (iii) have/ have had an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m². The PBAC noted the grandfathering restriction may need to stay in place for longer than the standard timeframe (i.e., more than 12 months), depending on the transition of other treatments for Fabry disease to the PBS.
- 7.5 The PBAC considered the proposed place in therapy for migalastat in patients over 12 years of age with an amenable mutation was appropriate and reiterated its previous recommendation that the requirement for at least 12 months of ERT prior to initiating migalastat could be removed.

- 7.6 The PBAC noted longer term clinical data for ATTRACT and FACETS were provided in the submission (up to 8.6 years follow up). The PBAC noted the longer-term data were inconsistent and confounded, but considered there may be some limited evidence that ERT and migalastat have similar outcomes in terms of renal function. However, the PBAC considered that, overall, the claim that migalastat is non-inferior to ERT remained insufficient.
- 7.7 The PBAC noted the submission proposed a [REDACTED] % price reduction to the unit cost of migalastat on the LSDP (ex-manufacturer price (EMP) of \$|per pack) which reduced the cost per patient per year from \$| to \$| assuming 13.04 packs per year. The PBAC noted the financial estimates were based on a cost per patient per year of \$| assuming 12 packs per year.
- 7.8 The PBAC noted the proposed cost of migalastat was higher than recommended in December 2022 but considered that, on balance, noting the high clinical need for ongoing access to funded treatments for Fabry disease, migalastat was likely to be of high but acceptable cost effectiveness for the population of patients with evidence of organ involvement/injury with a cost per patient per year of \$| as proposed in the financial estimates.
- 7.9 The PBAC advised the number of eligible patients with evidence of organ involvement/injury that would be treated with migalastat on the PBS was high but reasonable (< 500 in Year 1, increasing to < 500 in Year 6, see Table 11). The PBAC considered the estimated number of treated patients accounted for the addition of criteria to allow (i) patients with significant gastrointestinal symptoms and cerebrovascular disease to access treatment with migalastat (as discussed in paragraph 7.3) and (ii) eligible ERT patients to transition to PBS-subsidised migalastat (as discussed in paragraph 7.4).
- 7.10 The PBAC considered a risk sharing arrangement with expenditure caps defined by the revised financial estimates (as outlined in paragraph 7.9) with a 100% rebate for any cost over the expenditure caps would appropriately manage the risk of use outside the restriction criteria.
- 7.11 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 Fabry disease without evidence of organ involvement/injury. The PBAC noted earlier use was likely to result in a significant number of additional years of treatment at a high cost per patient. Additionally, the PBAC noted the estimated number of patients that would access treatment in the earlier disease setting relied on a number of poorly supported assumptions and was highly uncertain.
- 7.12 The PBAC previously advised that migalastat is not suitable for prescribing by nurse practitioners.

- 7.13 The PBAC previously recommended that the Early Supply Rule should apply to migalastat.
- 7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for migalastat:
- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative treatments for Fabry disease;
 - The treatment is not expected to address a high and urgent unmet clinical need because of the availability of alternative treatments for Fabry disease;
 - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item and new indication:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands	Manufacturer
MIGALASTAT						
migalastat 123 mg capsule, 14	NEW	1	14	5	Galafold	Amicus Therapeutics

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Restriction summary: New 1/ Treatment of concept: New 2
Indication: Fabry disease
Treatment Phase: Initial treatment
Clinical criteria:

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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 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:
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 MRI or echocardiogram data, in the absence of hypertension, (ii) Significant life-threatening arrhythmia or conduction defect. 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
Treatment criteria:
Must be treated by a physician with expertise in the management of Fabry disease
AND
Population criteria:
Patient must be at least 12 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) a completed authority prescription form; 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).

<p>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 authority to prescribe should 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</p>
<p>Restriction summary: New 3/ Treatment of concept: New 4</p>
<p>Indication: Fabry disease</p>
<p>Treatment Phase: Continuing treatment</p>
<p>Clinical criteria: Patient must have received prior PBS-subsidised treatment with this drug for this condition.</p>
<p>AND</p>
<p>Clinical criteria: Patient must have demonstrated clinical improvement or stabilisation of condition, the details of which must be kept with the patient's record.</p>
<p>AND</p>
<p>Clinical criteria: Patient must not have developed another life threatening / severe disease where long term prognosis is unlikely to be influenced by migalastat.</p>
<p>AND</p>
<p>Treatment criteria: Must be treated by a physician with expertise in the management of Fabry disease</p>
<p>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).</p>
<p>Restriction summary: New 5/ Treatment of concept: New 6</p>
<p>Indication: Fabry disease</p>
<p>Treatment Phase: Grandfather arrangement (transition from LSDP-funded Fabry disease therapy)</p>
<p>Clinical criteria: Patient must have previously received treatment with this drug for this condition funded under the Australian Government's Life Saving Drugs Program (LSDP) prior to (PBS listing date) OR 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)</p>
<p>AND</p>
<p>Clinical criteria: Patient must have a documented migalastat amenable galactosidase alpha (GLA) gene variant prior to commencing treatment with this drug.</p>
<p>AND</p>

Clinical criteria:
Patient must have/ have had an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m ² prior to commencing treatment with this drug.
AND
Treatment criteria:
Must be treated by a physician with expertise in the management of Fabry disease
AND
Population criteria:
Patient must be at least 12 years of age.
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 in writing and must include: (1) a completed authority prescription form; 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: 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 authority to prescribe should 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

The restriction 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

Amicus are pleased that the PBAC has agreed that Galafold is a cost-effective medication for the treatment of Fabry disease in amenable patients under the proposed arrangement. We

will work with the department to make this important therapy available through the PBS as quickly as possible.

Addendum to the March 2024 PBAC PSD:

4.01 MIGALASTAT,

**Capsule containing migalastat hydrochloride 150 mg
Galafold[®],
Amicus Therapeutics Pty Ltd**

11 Background

- 11.1 At its March 2024 meeting, the PBAC recommended the listing of migalastat for the treatment of Fabry disease in patients aged 12 years of age and older who have an amenable mutation and evidence of organ involvement/injury (including severe gastrointestinal symptoms, uncontrolled chronic pain, renal disease, cardiac disease, ischaemic disease and cerebrovascular disease).
- 11.2 Subsequent to the March 2024 meeting, the sponsor requested the PBAC consider:
- An amendment to the restriction to include an additional cardiac criterion; and
 - An amendment to allow a less than 100% rebate for any costs over the expenditure caps.

12 Requested listing

- 12.1 The sponsor stated that they have received feedback from clinicians experienced in treating Fabry disease that the cardiac criteria could be improved to include late gadolinium enhancement or low T1 changes on cardiac magnetic resonance imaging (MRI). Clinicians have advised the sponsor that this testing is covered by MBS item 63385¹⁴. The sponsor did not request an increase in patient numbers to include this amendment.

13 Financial management – Risk Sharing Arrangement

- 13.1 The PBAC previously considered a risk sharing arrangement with expenditure caps defined by financial estimates with a 100% rebate for any cost over the expenditure caps would appropriately manage the risk of use outside the restriction criteria (paragraph 7.10).
- 13.2 Subsequent to the March 2024 PBAC meeting, the sponsor indicated the addition of the clinical criterion ‘Patient must have significant Fabry-related gastrointestinal symptoms despite the use of the recommended doses of appropriate pharmacological therapies’ (paragraph 7.3) may increase the number of patients likely to be treated

¹⁴ “MRI—scan of cardiovascular system for congenital disease of the heart or a great vessel”

with migalastat. However, the PBAC had considered that the number of eligible patients, which was high but reasonable, accounted for the additional criterion regarding gastrointestinal symptoms (paragraph 7.9).

- 13.3 As an alternative to increasing the patient numbers, was PBAC was asked to consider whether a rebate of less than 100% would be acceptable.

14 PBAC Outcome

- 14.1 The PBAC recommended the requested amendment to the cardiac restriction criterion to include late gadolinium enhancement or low T1 changes on cardiac magnetic resonance imaging. The PBAC noted this requested change to the restriction was consistent with the Fabry Australia Treatment Review White Paper (now published as Nicholls 2024). The PBAC considered this amendment was clinically appropriate and it was unlikely to increase the number of eligible patients.
- 14.2 The PBAC reiterated its consideration that the number of eligible patients with evidence of organ involvement/ injury was high but reasonable and accounted for patients with significant gastrointestinal symptoms (paragraph **Error! Reference source not found.**). However, the PBAC considered it would be reasonable to allow a rebate of less than 100% in the first 2 years of listing to share any residual uncertainty regarding the eligible patient numbers, particularly the uncertainty associated with the transition from the LSDP to the PBS. The PBAC advised that any rebate would need to require the sponsor to rebate the majority of the cost of migalastat.

Outcome:

Recommended

15 Recommended listing

- 15.1 Amend restriction provided in paragraph **Error! Reference source not found.** (additions in italics):

Patient must have Fabry-related cardiac disease confirmed by at least one of the following: (i) Left ventricular hypertrophy, as evidenced by cardiac MRI or echocardiogram data, in the absence of hypertension, (ii) Significant life-threatening arrhythmia or conduction defect. (iii) <i>Late gadolinium enhancement or a low T1 on cardiac MRI</i> OR

16 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.

17 Sponsor's Comment

Amicus is pleased to have found a solution that works for patients and the Commonwealth allowing broader access to Galafold (Migalastat) for eligible Fabry patients in Australia.