

7.12 MIGALASTAT

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

1 Purpose of Application

- 1.1 The minor resubmission requested a Section 100 (Highly Specialised Drug Program) Authority Required listing for the treatment of Fabry disease.

2 Requested listing

- 2.1 The minor resubmission proposed no changes to the requested listing provided in the major March 2017 submission.

3 Background

- 3.1 Migalastat registered on the ARTG on 11 August 2017, with the indication:

Migalastat is indicated for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α -galactosidase A deficiency) and who have an amenable mutation.

- 3.2 A major submission for migalastat was considered by the PBAC at its March 2017 meeting. The PBAC deferred making a recommendation on the listing of migalastat for Fabry Disease pending the outcome of the TGA evaluation.

- 3.3 A minor resubmission for migalastat was considered by the PBAC at its July 2017 meeting and was not recommended for listing. In making this decision, the PBAC was uncertain about the submission's clinical claim of non-inferior comparative effectiveness compared with enzyme replacement therapy (ERT).

4 Current situation

- 4.1 The current minor resubmission aimed to address issues raised by the PBAC in their consideration of migalastat at the July 2017 meeting. The main concerns in the PBAC's previous consideration of migalastat, and the approach taken in the current minor resubmission to address those concerns, are summarised in Table 1.

Table 1: PBAC matters of concern in previous consideration (July 2017)

Matters of concern	How the resubmission addresses it
<p>The outcomes of the trials did not provide confidence in either the superior clinical effectiveness of migalastat over placebo or the non-inferior clinical effectiveness of migalastat compared to ERT (para 5.3)</p>	<p>The resubmission stated (p3) that the purpose of the minor submission was to present “newly-available long-term clinical data in patients with Fabry disease treated with migalastat.”</p> <p>The resubmission presents some additional long-term clinical data generated by an “integrated analysis” of the results of the ATTRACT study, FACETS study, phase 2 studies, and extension study AT10001-041.</p>
<p>The PBAC noted that the minor resubmission and the comments from consumers discussed the advantages of an oral treatment option compared with the current infusible treatments. However, the PBAC noted that the submission had not formally analysed any associated benefits to patients using migalastat rather than ERT. (para 5.5)</p>	<p>Not addressed in the resubmission. The pre-PBAC stated: Elimination of the need for hospital based infusions due to the uptake of migalastat will be cost-saving to hospital and state government budgets. Whilst the magnitude of these savings have not been quantified or considered in the pricing of migalastat, Amicus considers this to be one of the many key benefits of migalastat relative to its ERT comparators along with the reduction in the burden of IV infusions for health care professionals, patients and their caregivers. These benefits were discussed qualitatively in the major PBAC submission for migalastat, which was lodged in November 2016.</p>
<p>The PBAC did not accept the submission’s clinical claim of non-inferiority versus ERT and therefore the basis for determining the equi-effective doses and the cost-minimisation approach was also not accepted (para 5.7)</p>	<p>An economic analysis was not provided in the resubmission. The same proposed ex-manufacturer price was provided in the PB11b form for this and the July 2017 resubmission. It was assumed that the approach is unchanged from the July 2017 resubmission, with cost-minimisation against agalsidase alfa and agalsidase beta, weighted according to market share at the migalastat cost of \$██████ per patient per year.</p> <p>This resubmission stated that the clinical claim of non-inferiority versus ERT is better supported.</p>
<p>The PBAC noted that the size of potential savings to Government depends on the methods by which the patient numbers and market share of ERTs are calculated. In addition, the PBAC remained concerned that risks which may impact on the financial cost include:</p> <ul style="list-style-type: none"> • the potential for unintended use in patients with non-amenable mutations, related to the Committee’s earlier concerns about the performance of testing; and • migalastat being used in combination with, rather than instead of, ERT, given their different mechanisms of action, as discussed in the March 2017 PBAC meeting. <p>Overall, at the price proposed in the submission, the PBAC considered that the claims of cost saving, or even cost-neutrality, may not be realised. (para 5.8)</p>	<p>The resubmission stated (p7):</p> <p><i>“Amicus would also like to reiterate that the company is committed to negotiating a price with the LSDP [Life Savings Drug Program] that provides cost-savings to the government”</i></p>

Source: Paragraph references refer to the July 2017 migalastat Public Summary Document.

4.2 The current minor resubmission was largely unchanged from the minor submission considered at the July 2017 PBAC meeting, and presented:

- Updated TGA status
- Additional discussion of the patient relevance of the endpoint glomerular

filtration rate (GFR), and the GFR results from the ATTRACT study

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from individuals (10) and Fabry Australia via the Consumer Comments facility on the PBS website. The comments, including the perspective of patients with or without the amenable mutations, described the benefits of treatment such as being a tablet compared to the current treatments that result in avoiding the physical and time burden of fortnightly intravenous infusion, which would improve people's quality of life.

5.3 Clinicians with experience with treating patients with Fabry disease and using migalastat provided further information on the clinical place and use of migalastat. While the decision to treat a patient is an individual decision with their doctor, older patients or patients with more severe disease would more likely remain on ERT. In regards to determining the amenability of a patient for the oral treatment, the clinicians considered that there was not a high risk of patients being inappropriately started on migalastat. If a patient was unresponsive after treatment with migalastat, they would switch to ERT soon after. Chaperone therapy, such as migalastat with ERT, has been postulated but there was little data to support this treatment regimen. The clinicians considered that if clinical criteria for migalastat were similar as for the currently subsidised treatments, there is not likely to be an increase in the number of patients. Compared to ERT, the clinicians discussed the reduced treatment burden for patients and reduced resource use in treatment centres.

Clinical trials

5.4 The minor resubmission was largely based on data from the ATTRACT head-to-head trial comparing migalastat to ERT in treatment-experienced patients (ITT, n=60; mITT amenable, n=52) and the FACETS head-to-head trial comparing migalastat to placebo in treatment-naïve patients (ITT, n=67; mITT amenable, n=50). Both studies had been presented to PBAC previously.

5.5 The minor resubmission discussed results from study AT-1001-041, an open-label extension (OLE) study that enrolled patients from ATTRACT, FACETS and a Phase 2 study called FAB-CL-205. The March 2017 submission noted that the study was terminated for administrative reasons and patients subsequently enrolled in ongoing OLE AT1001-042. While the March 2017 submission noted that the OLEs existed, the

results do not appear to have been presented to the PBAC previously, and these studies have not been evaluated.

- 5.6 In addition, the minor resubmission included a number of tables of results and analyses in Attachment 1 of the resubmission. This attachment is provided as the source for some of the results presented in the minor submission in support of the stabilisation of GFR after long-term migalastat treatment. The sources of the numbers presented in Attachment 1, and any methods for the analyses presented, are unclear and these results could therefore not be validated.
- 5.7 The pre-PBAC response provided a summary of the re-analyses and the studies from which the data were sourced. The pre-PBAC response stated that most of these results were not presented in the original migalastat submission as the analyses were not pre-specified in a statistical analysis plan.

Stabilisation of GFR in the ATTRACT study

- 5.8 The key GFR results for the amenable population in the ATTRACT study are presented below. The data for all patients were previously presented to the PBAC in the March major submission (Table 22, p52 of the March 2017 migalastat submission) and the subsequent July minor submission (Table 1, p9 of the July 2017 migalastat submission). The Secretariat noted that results for the renal impairment subgroup (baseline eGFR<90) do not appear to have been presented in this way to the PBAC previously. This appears to have been a post-hoc subgroup analysis, however the source for these results is not clear and therefore the validity of these figures could not be confirmed. The Pre-PBAC response confirmed that these subgroup analyses were in fact pre-specified in the ATTRACT protocol, with the results presented in the final clinical study report.

Table 2 Summary of Annualized Change in GFR: Study AT1001-012, ITT-amenable Population

GFR (ml/min/1.73 m ² /yr)	eGFR _{CKD-EPI} annualised change from baseline		mGFR _{Iohexol} annualized change from baseline	
	All patients	Baseline eGFR<90	All patients	Baseline eGFR<90
Migalastat LS Mean (n)	-0.40 (n=34)	-3.33 (n=20)	-4.35 (n=34)	-3.51 (n=20)
ERT LS Mean (n)	-1.03 (n=18)	-9.05 (n=8)	-3.24 (n=18)	-7.96 (n=7)
LS Mean Difference (95% CI)	+0.63 (-2.57, 3.83)	+5.72 (-1.87, 13.30)	-1.12 (-6.74, 4.51)	+4.46 (-0.66, 9.57)

Abbreviations: ERT=enzyme replacement therapy; GFR=glomerular filtration rate; LS=least squares; Notes: LS Mean and 95% CI based on ANCOVA that includes treatment, baseline GFR, sex, age, and 24-hr urine protein. Source: Table 1, p4 of the minor resubmission

Stabilisation of GFR after long-term migalastat treatment

- 5.9 The minor resubmission stated that the longer-term effect of migalastat on renal function was assessed in the extension arms/studies of the Phase 2 and Phase 3 studies, and presented the following table.

5.10

Table 3. Summary of annualised change in GFR after treatment with migalastat at different timepoints

Timepoint	Annualised change in GFR _{CKD-EPI} (ml/min/1.73 m ² /yr)	Source	Population
1.5 years	-0.4 (n=34)	ATTRACT study	Patients switched from ERT to migalastat
2.5 years	-1.7 (n=31)	ATTRACT study	ERT switch patients continuing into the 12-month extension arm of the ATTRACT study
3.4 years (range: 1.5-4.9 years)	-0.69 (n=41)	Integration of FACETS and AT1001-041*	ERT naive patients continuing from the placebo-controlled FACETS
8.2 years (maximum 9.3 years)	-0.67 (n=12)	Integration of phase 2 studies and AT1001-041*	Patients completing phase 2 studies (FAB-CL-201, FAB-CL-202, FAB-CL-203, or FAB-CL-204) on varying doses and regimens of migalastat.
4-5 years	+0.24 (n=11)	AT1001-041*	Patients completing phase 2 studies (FAB-CL-201, FAB-CL-202, FAB-CL-203, or FAB-CL-204) on 150 mg migalastat QOD.

Source: Table 2, p6 of the minor resubmission

*as noted above, the results from AT1001-041 and the 'integration' of this with other studies, could not be validated

Clinical claim

5.11 The clinical claim remained unchanged from the March 2017 submission and July 2017 resubmission. This resubmission stated 'The evidence presented in this minor submission supports the long-term efficacy of migalastat in stabilising renal function in patients with Fabry disease'.

5.12 At its March 2017 meeting, the PBAC did not accept the major submission's claim of non-inferiority compared with the comparator, enzyme replacement therapy (ERT). However, the PBAC considered that it was reasonable to accept the claim of non-inferior comparative safety of migalastat compared to ERT.

Economic analysis

5.13 An economic analysis was not provided in this resubmission. The ex-manufacturer price remained unchanged from the July 2017 resubmission. It was therefore considered that the cost-minimised approach was unchanged from the July 2017 resubmission. The July 2017 resubmission proposed cost of \$ [REDACTED] per patient per year with the weight of ERT use based on the proportions of agalsidase alfa and agalsidase beta used in the ATTRACT trial (66.1% and 33.9%, respectively).

5.14 The pre-PBAC response reiterated that migalastat will provide cost-savings to the Government by [REDACTED], and by avoiding the costs of hospital-based infusions.

Drug cost/patient/year: \$ [REDACTED]

Estimated PBS usage & financial implications

- 5.15 The estimated PBS usage & financial implications were not directly discussed in this resubmission. The calculation of estimated PBS usage and financial implications were considered to be unchanged from the previous submission.
- 5.16 The March 2017 major submission stated that there were at least 280 Fabry patients registered in Australia.
- 5.17 The July 2017 Public Summary Document (paragraph 5.8) noted the following concerns:

The minor resubmission claimed that there would a cost saving to Government by subsidising migalastat. The PBAC noted that the cost of migalastat was different to agalsidase alfa and agalsidase beta. The PBAC noted that the size of potential savings to Government depends on the methods by which the patient numbers and market share of ERTs are calculated. In addition, the PBAC remained concerned that risks which may impact on the financial cost include:

- the potential for unintended use in patients with non-amenable mutations, related to the Committee’s earlier concerns about the performance of testing; and
- migalastat being used in combination with, rather than instead of, ERT, given their different mechanisms of action, as discussed in the March 2017 PBAC meeting.

Overall, at the price proposed in the submission, the PBAC considered that the claims of cost saving, or even cost-neutrality, may not be realised.

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC did not recommend the Section 100 (Highly Specialised Drug Program) Authority Required 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 enzyme replacement therapy (ERT) remained uncertain and could not be supported.
- 6.2 The PBAC reiterated that agalsidase alfa and agalsidase beta (used in ERT) were the appropriate comparators for migalastat. These two treatments are not listed on the PBS and have not been considered to be cost-effective for listing on the PBS.
- 6.3 The PBAC noted the additional clinical evidence provided in the resubmission was derived from analysis of the ATTRACT study, FACETS study, phase 2 studies, and the extension study AT10001-041. The PBAC recognised that Fabry disease is a rare condition leading to difficulties undertaking clinical trials in this patient population, and recalled that it had considered annualised change in GFR was a reliable marker

of long-term kidney outcome. The PBAC noted that while the clinical evidence in this resubmission had not been evaluated and the data was based on small numbers of patients in the uncontrolled trials, the long-term preservation of GFR in the aggregated data and ease of administration compared to ERT suggested there is likely to be a clinical place for migalastat in place of ERT for some patients.

- 6.4 However, the PBAC considered that the arguments presented in the minor resubmission supporting the claim of non-inferior effectiveness versus the main comparator did not change the view of the Committee formed at the March 2017 and July 2017 meetings. Therefore, the PBAC reiterated that it could not accept the clinical claim of non-inferior effectiveness compared with the primary comparator of ERT, in either treatment naïve patients or in treatment experienced or switch patients.
- 6.5 The PBAC recalled that, at its March 2017 meeting, it considered that with the currently available evidence in treatment naïve patients and in treatment experienced or switch patients, it was reasonable to accept the claim of non-inferior comparative safety of migalastat compared to ERT.
- 6.6 The PBAC noted that the minor resubmission and the comments from consumers discussed the advantages of an oral treatment option compared with the current infusible treatments. The input from clinicians with experience in treating patients with Fabry disease provided clarity on the use of migalastat in the Australian context. The PBAC noted that the submission had not formally analysed any associated benefits to patients using migalastat rather than ERT.
- 6.7 The PBAC recalled that it had agreed that a cost-minimisation approach would be the appropriate economic comparison based on the submission's clinical claim of non-inferiority compared with ERT. However, as noted above, the PBAC did not accept the submission's clinical claim of non-inferiority versus ERT and therefore the basis for determining the equi-effective doses and the cost-minimisation approach were also not accepted.
- 6.8 The minor resubmission claimed that there would be a cost saving to Government by subsidising migalastat. As the resubmission did not formally discuss the estimated PBS usage & financial implications, the PBAC reiterated its view from the July 2017 meeting that at the price proposed in the resubmission, the claims of cost saving, or even cost-neutrality may not be realised.
- 6.9 The PBAC noted that this submission is eligible for an Independent Review.
- 6.10 Though matters relating to the subsidy of medicines outside the PBS are not a matter for the PBAC, should non-PBS subsidy approaches be considered, the PBAC wished to advise the Minister that:
 - The PBAC considered that migalastat does provide a clinical benefit in stabilising

renal function in patients with Fabry disease. This minor resubmission stated 'renal function represents one clinical manifestation of Fabry disease, and it is very likely that the benefits of therapy will also extend to other organ classes such as the cardiovascular system.' The PBAC considered that this claim has not been substantiated. The submissions for migalastat did not address whether intermediate outcomes presented in clinical trials resulted in increased survival and/or improved quality of life. Agalsidase alfa and agalsidase beta were added to the LSDP in 2004. When the PBAC considered a report on the updated literature review of the comparative efficacy and safety of agalsidase alfa versus agalsidase beta at the November 2009 meeting, the published trials and their long-term extensions appeared to support the efficacy of agalsidase alfa and agalsidase beta (in terms of both a reduction in clinical symptoms as well as an improvement/stabilisation of surrogate endpoints). Some of these surrogate endpoints were common to trials with migalastat.

- The PBAC had not accepted the clinical claim of non-inferior effectiveness compared with the primary comparator of ERT, in either treatment naïve patients or in treatment experienced or switch patients, nor the basis of the cost-minimisation analysis. The PBAC noted the concerns of the evaluators and the ESC in regards to the methodology and assumptions of the cost-minimisation analysis, presented in the March 2017 major submission. The PBAC noted the Department would have data on the patient characteristics and the current use of ERT, which would inform certain assumptions, such as deriving the weight based annual cost of ERT.
- The PBAC noted that the cost of migalastat was different to agalsidase alfa and agalsidase beta, and that the costs of agalsidase alfa and agalsidase beta presented in previous submissions are different. The PBAC noted that the sponsor offered a █% price reduction between the March 2017 and July 2017 submissions. If migalastat were to be subsidised by the Commonwealth, the Minister may wish to consider 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, measured over a one to two year time period, with a further significant price reduction reflective of the uncertainty around the claim of non-inferiority to ERT.
- The pre-PBAC response for this resubmission emphasised migalastat will provide Fabry patients with a safe and effective treatment option with several advantages over current enzyme replacement therapies (ERTs), such as:
 - eliminating the burden associated with ERT administration, for patients and their caregivers
 - reducing the risk of experiencing infusion associated reactions (IARs) or immunogenic reactions
 - facilitating dosing to a stable drug concentration, with broad tissue distribution.

The PBAC agreed that there would be an advantage of an oral treatment over an

infusible medicine. The Committee noted patients with Fabry disease would likely continue to be regularly followed by clinicians and that the evaluation of the March 2017 submission had discussed possible requirements for patient monitoring before and during migalastat treatment. As the sponsor had not quantified any associated benefits or additional costs for patients using migalastat rather than ERT, the PBAC considered at this time, valuing migalastat compared to ERT only on a medicine cost basis was appropriate.

- The PBAC remained concerned by the potential for unintended use in patients with non-amenable mutations. The PBAC recalled that the pre-PBAC response to the July 2017 resubmission proposed that certain factors could be considered in determining the price of migalastat, including the cost of therapy in patients who receive migalastat but do not demonstrate a response at 6 months.
- The PBAC recalled from the July 2017 meeting, although the Committee's concerns regarding determining eligibility for migalastat remained from the March 2017 consideration, the PBAC did not consider it necessary to assess codependent testing for the MBS in the context of any Commonwealth subsidy of this medicine. If concerns arise later about testing to determine eligibility, advice of the Medical Services Advisory Committee could be sought.
- The final version of Product Information (PI) for migalastat states that migalastat is not intended for use in combination with enzyme replacement therapies (ERTs). However, the PBAC remained concerned of the potential for migalastat to be used in combination with, rather than instead of, ERT, given their different mechanisms of action, as discussed at the March 2017 PBAC meeting. The PBAC considered that eligibility criteria for subsidised treatment for Fabry disease should exclude concomitant use of multiple medicines. Further, the Minister may consider a Risk Share Agreement to ensure that, as reiterated by the sponsor in the pre-PBAC response, subsidy of migalastat would provide cost saving to Government.

Outcome:

Rejected

7 Context for Decision

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

8 Sponsor's Comment

Amicus thanks the PBAC for its consideration of migalastat to treat Fabry disease. Based on the Committee's recognition that migalastat is clinically effective in stabilising renal function in patients with Fabry disease, we look forward to liaising with the Life Saving Drugs Program to ensure that this novel oral therapy is made available to eligible Australian Fabry disease patients.