

## **4.03 MIGALASTAT**

### **Capsule containing migalastat hydrochloride, 150 mg, Galafold<sup>®</sup>, 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 March 2017 submission.

#### **3 Background**

- 3.1 At the time of PBAC consideration, migalastat was not yet registered by the TGA. Available to the Committee was a positive TGA Delegate's Overview and the Advisory Committee on Medicine's (ACM's) resolution from its June 2017 meeting.
- 3.2 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 The minor resubmission sought to address the concerns arising from the PBAC's consideration of the major submission at the March 2017 meeting, including:
- The role of the GLP-HEK assay in determining the amenability of GLA mutations;
  - The claim of non-inferior effectiveness versus the main comparator, enzyme replacement therapy (ERT);
  - The economic and budget implications of migalastat to the government; and
  - An update on the TGA's evaluation of migalastat.
- 3.4 A summary of the previous and current submissions is provided in Table 1.

**Table 1: Summary of the previous submission and current minor resubmission**

	March 2017 submission	Current minor resubmission
Requested PBS listing	Section 100 (Highly Specialised Drug Program) Authority Required listing for the treatment of Fabry Disease in patients aged 16 and over who have an amenable mutation. Other drugs subsidised for treatment of Fabry disease are not listed on the PBS and are listed on the Life Saving Drugs Program (LSDP).	Unchanged
Requested price per patient per year	\$ [REDACTED]	\$ [REDACTED] This is a [REDACTED] % reduction on the price proposed in the main submission.
Comparator	<ul style="list-style-type: none"> <li>Agalsidase alfa and agalsidase beta</li> </ul> <p><b>PBAC comment:</b> The PBAC recognised that agalsidase alfa and agalsidase beta are not listed on the PBS and have not been considered to be cost-effective for listing on the PBS, but agreed that these two treatments were the appropriate comparators (para 7.2).</p>	Unchanged
Clinical evidence	<ul style="list-style-type: none"> <li>ATTRACT: head-to-head trial comparing migalastat to ERT in treatment-experienced patients. (ITT, n=60; mITT amenable, n=52)</li> <li>FACETS: head-to-head trial comparing migalastat to placebo in treatment-naïve patients (ITT, n=67; mITT amenable, n=50).</li> </ul> <p><b>PBAC comment:</b> the PBAC noted the concerns raised by ESC (small sample size, post-hoc analyses, variability in baseline disease characteristics) but recognised that Fabry disease is a rare condition leading to difficulties undertaking clinical trials in this patient population (para 7.3). The PBAC noted the planned outcomes of on-going Open-Label Extension Study of the Long-Term Effects of Migalastat HCL in Patients With Fabry Disease (ClinicalTrials.gov Identifier: NCT02194985) (para 7.13).</p>	<p>No additional clinical evidence presented for the use of migalastat in Fabry disease.</p> <p>The submission states the trial NCT02194985 is ongoing and is not due to complete until October 2019...it is not expected that the trial outcomes will differ greatly to those already presented for the pivotal trials in the major submission given that the purpose of migalastat is to stabilise disease and all patients in the trial receive migalastat (i.e. there is no control arm in these trials).</p>
Key effectiveness data	<ul style="list-style-type: none"> <li>ATTRACT: annualised rate of change in GFR over 18 month treatment period.</li> <li>FACETS: proportion of patients who achieved a more than 50% reduction in GL3 inclusions per kidney IC at month 6.</li> </ul> <p><b>PBAC comment:</b> The PBAC considered that change in GFR is a reliable marker of long-term kidney outcome, but that the non-inferiority criterion had not been fully justified (para 7.4). The PBAC noted that the magnitude of any benefit for the FACETS outcome compared to placebo was very imprecise and consistent with no effect (para 7.6).</p>	No additional clinical evidence presented for the use of migalastat in Fabry disease.

Public Summary Document – July 2017 PBAC Meeting

	March 2017 submission	Current minor resubmission
Clinical claim	<p>Non-inferior comparative effectiveness and safety over enzyme replacement therapy (ERT) based on surrogate biomarker outcomes.</p> <p><b>PBAC comment:</b> The PBAC did not accept the submission's claim of non-inferiority compared with ERT (para 7.11), as the non-inferiority criterion had not been fully justified...the relative effectiveness of ERT and migalastat is uncertain (para 7.4).</p> <p>The PBAC noted that the primary outcome in FACETS was the proportion of patients who achieved a response...but that the magnitude of any benefit for this outcome, compared to placebo, was very imprecise and consistent with no effect [in treatment-naïve patients] (para 7.6).</p> <p>The PBAC considered 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 compared to ERT (para 7.8).</p>	No change.
Economic evaluation	Cost-minimisation against agalsidase alfa and agalsidase beta, weighted according to market share.	The new proposed price is weighted according to the proportions of ERT products used in the ATTRACT trial. The pre-PBAC response 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 and any additional costs of monitoring and of initiating treatment.
Risk sharing arrangement	The submission stated that the sponsor is "willing to discuss the negotiation of an agreement, at the appropriate time, to facilitate the listing of migalastat". The submission does not present any details of the proposed risk share arrangement. The ESC noted that a cap on the total costs of Fabry disease treatment could be considered to share the risk of the uncertain population size (para 6.36).	The pre-PBAC response discussed various mechanisms to mitigate against risks.
PBAC decision	Defer. <b>PBAC Comment:</b> (para 7.1) The PBAC deferred making a recommendation on the listing of migalastat for Fabry Disease pending the outcome of the TGA evaluation.	N/A.

For more detail on PBAC's view, see section 5 "PBAC outcome."

## 4 Consideration of the evidence

### Sponsor hearing

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

**Consumer comments**

4.2 The PBAC noted and welcomed the input from individuals (11), Rare Voices Australia and Fabry Australia via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with a tablet compared to the current treatments such as avoiding the physical and time burden of fortnightly intravenous infusion, which would improve people's quality of life.

**Consideration of the minor resubmission**

4.3 The concerns raised in the PBAC's previous consideration of migalastat, and the current minor resubmission's attempts to address those concerns, are summarised in Table 2.

**Table 2: The minor resubmission's attempts to address the PBAC's concerns regarding migalastat**

Matters of concern	How the minor resubmission addresses it
"The PBAC considered that the non-inferiority criterion had not been fully justified." (para 7.4).	The sponsor has provided an argument for the robustness of the non-inferiority criterion, including advice from the European Medicines Agency on the study design and comparability criteria of the trials. No new data provided.
"The PBAC also noted that there was considerable variability in GFR relative to any observed treatment effect (making identification of responders problematic). The PBAC considered, given the wide confidence intervals in the difference between migalastat and ERT, that the relative effectiveness of ERT and migalastat is uncertain." (para 7.4).	The sponsor claims that variability in GFR has been observed in a number of studies apart from FACETS and ATTRACT, and states that the eGFR results are more meaningful than the mGFR as more frequent results are available. The confidence intervals for eGFR are narrower than for mGFR.
"...the PBAC did not accept the submission's claim that, based on the change in left ventricular mass index (LVMI), migalastat was superior to ERT in reducing LVMI in Fabry patients" (para 7.5).	The sponsor acknowledges that the evidence is not strong enough to support a superiority claim, but maintains it is adequate for a non-inferiority claim.
"The PBAC recalled that it has previously considered the clinical relevance of left ventricular mass as an outcome in Fabry patients to be uncertain." (para 7.5).	The sponsor has provided an argument for the clinical relevance of left ventricular hypertension in Fabry patients, supported by studies of the natural history of the disease and by data from ATTRACT.
"The PBAC noted that primary outcome in FACETS was the proportion of patients who achieved a response, defined as more than a 50% reduction in GL3 inclusions per kidney IC at Month 6, but that the magnitude of any benefit for this outcome, compared to placebo, was very imprecise and consistent with no effect." (para 7.6).	The pre-PBAC response discussed the ITT, pre-specified and post-hoc analyses of the FACETS trial.

Public Summary Document – July 2017 PBAC Meeting

<p>“...the PBAC raised concerns that the analytical and clinical validity of the test requirements for determining eligibility to migalastat, and particularly the GLP-HEK assay in informing the Galafold Amenability Table (GAT), has not been assessed in the context of Australian standard genetic testing.” (para 7.10).</p>	<p>The submission clarifies the role and accuracy of the GLP-HEK assay, including how the GLP-HEK assay has been validated and improved since it was used to recruit patients to FACETS and ATTRACT. The pre-PBAC response provided more information on the assay.</p>
<p>“The PBAC considered seeking the advice of the Medical Services Advisory Committee on the analytical and clinical validity of these requirements, and agreed that this should occur if, following future PBAC considerations, the PBAC were ever of a mind to advise the Minister of a favourable judgement regarding the comparative clinical effectiveness and safety of migalastat to ERT and placebo.” (para 7.10).</p>	<p>The minor resubmission stated that MSAC consideration of the assay is not warranted, as:</p> <ul style="list-style-type: none"> <li>• the accuracy, accessibility and reimbursement of the process by which a patient’s GLA mutation is determined has been established; and</li> <li>• the assessment of the mutation against the Galafold Amenability Table will be completely undertaken by the sponsor, and so there are no implications for the MBS.</li> </ul>
<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 a cost-minimisation analysis was inadequate. Given that the PBAC had previously considered the comparators not adequately cost-effective to allow listing on the PBS, the PBAC were of a mind to consider that migalastat would also not be adequately cost-effective to recommend listing on the PBS based on the evidence presented thus far.” (para 7.11).</p>	<p>The sponsor agreed with the PBAC’s advice from the original major submission that migalastat cannot be considered acceptably cost-effective for PBS listing because the comparator of ERT treatments themselves are not cost-effective.</p>
<p>“The PBAC considered that there may be a risk of migalastat being used in combination with, rather than instead of, ERT, given their different mechanisms of action, and that migalastat may be used after ‘failure’ of ERT. The PBAC considered that the claims of cost-neutrality are therefore questionable.” (para 7.12).</p>	<p>The pre-PBAC response stated the sponsor does not consider combination use to be a significant risk, as combination use is contraindicated in the PI and eligibility criteria to ensure migalastat is not used in combination with ERTs can be developed.</p>

**Estimated PBS usage & financial implications**

- 4.4 The major submission assumed that the increased cost of funding migalastat will be equal to the reduced market share of the two ERTs, resulting in zero net cost to Government, based on the original migalastat price (\$[REDACTED]). The minor resubmission claimed that the new proposed price would result in a cost saving of less than \$10 million over 5 years. The estimated value of the cost-offset of the ERTs was the same in both submissions.
- 4.5 The major submission calculated the total number of migalastat eligible patients by multiplying the amenability proportion (45%) by the [REDACTED] patients currently receiving ERT and the [REDACTED] grandfathered patients in Year 1. The grandfathered patients should all have amenable mutations (100%) and hence this underestimates the number of eligible patients. Similarly, the market share (30%) was applied to the [REDACTED] grandfathered patients in Year 1, which underestimated the uptake by new patients. The sponsor, in its Pre-Sub-Committee Response and pre-PBAC response considered in March 2017, and in the pre-PBAC response for this minor resubmission, stated that to exclude patients already receiving migalastat would have over-estimated the

number of eligible patients.

- 4.6 The minor resubmission claimed, in addition, that cost savings would have accrued from the reduction in the administration of ERT infusions and associated adverse events. The submission does not quantify these potential savings to Government. The pre-PBAC response stated that any reduction in hospital based infusions due to the uptake of migalastat will be cost-saving to hospital and state government budgets.

*For more detail on PBAC's view, see section 5 "PBAC outcome."*

## **5 PBAC Outcome**

- 5.1 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 was uncertain about the submission's clinical claim of non-inferior comparative effectiveness compared with enzyme replacement therapy (ERT).
- 5.2 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.
- 5.3 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 meeting. The PBAC reiterated that 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. The PBAC recognised that Fabry disease is a rare condition leading to difficulties undertaking clinical trials in this patient population, and considered annualised change in GFR was a reliable marker of long-term kidney outcome. However, the PBAC expressed concerns over the nature and the patient relevance of the outcome measured in the submitted evidence, the short duration over which these measures were followed up, and lack of clarity over the minimal clinically important difference in and statistical significance of the results presented. Therefore, the PBAC 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.
- 5.4 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.

- 5.5 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.
- 5.6 The PBAC noted that the minor resubmission and the pre-PBAC response provided further information on the GLP-HEK assay and the Galafold Amenability Table (GAT) used to determine if a mutation is amenable to treatment with migalastat. The TGA's ACM noted that there is a mechanism for removing from the list any mutations subsequently determined not to be amenable; this was not raised in the minor resubmission. Overall, although the concerns of the Committee regarding determining eligibility to 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.
- 5.7 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 was also not accepted.
- 5.8 The minor resubmission claimed that there would be 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.

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

**Outcome:**

Rejected

**6 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.

**7 Sponsor's Comment**

Amicus continues to work with the PBAC to ensure that migalastat is made available to Australian patients diagnosed with Fabry Disease who have an amenable mutation.