

## 5.04 MIGALASTAT, Capsules 150 mg, Galafold<sup>®</sup>, Amicus Therapeutics.

### 1 Purpose of Application

- 1.1 The submission requested a Section 100 (Highly Specialised Drugs 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).

### 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
MIGALASTAT CAPSULES 150 MG	14	3	\$ [REDACTED]	Galafold <sup>®</sup> Amicus Therapeutics

#### **Section 100 (Highly Specialised Drugs Program) Authority required**

Long-term treatment patients with a confirmed diagnosis of Fabry disease ( $\alpha$ -galactosidase A deficiency) and who have an amenable mutation (see Galafold Amenability Table)

- 2.1 The basis for listing is cost-minimisation against the enzyme replacement therapies (ERT), agalsidase alfa and agalsidase beta.
- 2.2 The proposed listing for migalastat was based on the current eligibility requirements of the LSDP and is restricted to patients aged 16 years and older who have an amenable GLA mutation according to an online panel (Galafold Amenability Table). Sequencing of the GLA gene is routinely used to confirm a genetic diagnosis of Fabry disease. There are hundreds of GLA mutations, but only 40% to 50% of these result in expression which is affected by (i.e. amenable to) migalastat. The ESC noted that the patients in the clinical trials were 16 years and older, but patients may be diagnosed and treated earlier, so there is a risk of leakage to children with the proposed restriction.
- 2.3 For patients harbouring mutations for which amenability cannot be judged using the online panel, access to migalastat is dependent on being diagnosed with an amenable GLA mutation using the GLP-HEK assay (Galafold Amenability Assay). The GLP-HEK Assay is not listed on the MBS, and is a new test specific to migalastat that was developed alongside the migalastat trials. The ESC agreed that the PBAC should consider whether this drug-test combination fulfils the requirements for an application under the process for co-dependent technologies. The FACETS and ATTRACT trials were based on a small sample size, and 25% and 7% of the patients did not have an amenable mutation in each of the trials respectively. The consequences of treating false-positive patients with migalastat (i.e. patients either missing out on potential benefits, if ERT would have been more effective, or experiencing harms) is unclear. The PSCR argued that 'In the unlikely event that a non-amenable patient is treated with migalastat, it is likely that they would be identified through lack of response to therapy and would subsequently be switched to ERT. It should also be noted that patients with mutations that provide uncertain

results would almost certainly be treated cautiously and would be unlikely to switch to migalastat.’ The ESC noted that treatment of non-amenable patient with migalastat delays access to effective treatments and would result in an increased cost to Government.

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

### **3 Background**

3.1 **TGA status at time of PBAC consideration:** The submission for migalastat hydrochloride capsules 150 mg (equivalent to migalastat 123 mg per capsule) was made under the Therapeutic Goods Administration (TGA)-PBAC Parallel Process. The TGA Delegate’s request for ACPM advice is expected in May 2017, and it is proposed that this will be reviewed at the ACPM meeting on 2 June 2017.

3.2 Migalastat has not been considered by the PBAC previously.

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

### **4 Clinical place for the proposed therapy**

4.1 The submission proposed migalastat as an alternative to ERT, agalsidase alfa and agalsidase beta for the treatment of Fabry disease in patients aged 16 and over with a migalastat amenable mutation.

4.2 The submission requested listing in the first-line (treatment naïve patients) and second-line (treatment experienced or switch patients) settings.

4.3 Fabry disease is a rare, X-linked genetic disorder caused by a deficiency in the enzyme alpha-galactosidase A ( $\alpha$ -Gal A). Deficiency of  $\alpha$ -Gal A results in accumulation in the body of globotriaosylceramide (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.

4.4 Treatment for Fabry disease in Australia is currently focused on correcting enzyme deficiencies through ERT. Migalastat acts directly on  $\alpha$ -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 younger than 16 years of age, and does not depend on amenability to a specific treatment.

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

### **5 Comparator**

5.1 The submission nominated ERTs, agalsidase alfa and agalsidase beta as the main comparators. The ESC considered that this is reasonable as ERTs (agalsidase alfa and agalsidase beta) are the treatments most likely to be replaced by migalastat.

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

## 6 Consideration of the evidence

### Sponsor hearing

6.1 There was no hearing for this item.

### Consumer comments

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

### Clinical trials

6.3 The submission is based on one head-to-head trial (ATTRACT) comparing migalastat to ERT (ITT, n=60; 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. A qualitative indirect comparison of migalastat and ERT using placebo as the common comparator in treatment-naïve patients was also presented as supportive evidence.

6.4 Details of the pivotal trials presented in the submission are provided in the table below

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Migalastat vs ERT</b>		
ATTRACT	Amicus Therapeutics. A Randomized, Open-Label Study to Compare the Efficacy and Safety of AT1001 and Enzyme Replacement Therapy (ERT) in Patients with Fabry Disease and AT1001-Responsive GLA Mutations, Who Were Previously Treated with ERT	Interim clinical study report. 18-month, 09 March 2015
	Amicus Therapeutics. A Randomized, Open-Label Study to Compare the Efficacy and Safety of AT1001 and Enzyme Replacement Therapy (ERT) in Patients with Fabry Disease and AT1001-Responsive GLA Mutations, Who Were Previously Treated with ERT	Clinical study report. 30-month, 31 March 2016
	Hughes D et al. Oral Pharmacological Chaperone Migalastat compared with enzyme replacement therapy in Fabry disease: 18 month results from the randomised Phase 3 ATTRACT study.	<i>J Med Genet.</i> 2016 (doi:10.1136/jmedgenet-2016-104178)
	Hughes D, et al. Long-term efficacy and safety of migalastat compared to enzyme replacement therapy in Fabry disease: Phase 3 study results. 2015	<i>Molecular Genetics and Metabolism</i> 2015, 114 (2): S57. [Abstract only]
<b>Migalastat vs placebo</b>		
FACETS	Amicus Therapeutics. A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacodynamics of AT1001 in Patients with Fabry Disease and AT1001-Responsive GLA Mutations	Clinical study report. 18-month, 14 January 2015
	Germain, D. P., Hughes, D. A., Nicholls, K., Bichet, D. G., Giugliani, R., Wilcox, W. R.,... & Bratkovic, D. (2016). Treatment of Fabry’s disease with the pharmacologic chaperone migalastat.	<i>New England Journal of Medicine</i> , 2016, 375(6), 545-555
	Nicholls K, et al. Phase 3 study of migalastat HCl for Fabry	<i>Molecular Genetics and</i>

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Trial ID	Protocol title/ Publication title	Publication citation
	disease: Stage 1 results.	<i>Metabolism</i> , 2013, 108(2), S70. [Abstract only]
	Germain, DP, et al. Treatment with Migalastat results in reduced levels of disease substrate and stable renal function in a Phase 3 study of Fabry disease.	<i>Journal of Inherited Metabolic Disease</i> , 2014, 37(1), S43. [Abstract only]
	Barlow C, et al. Phase 3 FACETS study of migalastat HCl for Fabry disease: Post hoc GLA mutation-based identification of subjects likely to show a drug effect.	<i>Molecular Genetics and Metabolism</i> , 2014, 111(2), S24. [Abstract only]
	Barlow, C. Clinical results using a GLP-validated pharmacogenetic test identifies subjects responsive to migalastat HCl in the FACETS study.	<i>Molecular Genetics and Metabolism</i> , 2014, 111(2), S23. [Abstract only]
	Germain, DP, et al. Subjects treated with migalastat continue to demonstrate stable renal function and reduced left ventricular mass index over 3 years in a long-term extension study of Fabry disease.	<i>Journal of Inherited Metabolic Disease</i> , 2015, 38(1), S56. [Abstract only]
	Schiffman R, et al., Improvement in gastrointestinal symptoms observed in the phase 3 FACETS (AT1001-011) study of migalastat in patients affected with Fabry disease.	<i>Molecular Genetics and Metabolism</i> , 2015 114(2), S103-S104. [Abstract only]
	Germain DP., et al. Efficacy of migalastat in a cohort of male patients with the classical form of Fabry disease in a phase 3 study.	<i>Journal of Inherited Metabolic Disease</i> , 2016, 39: S219. [Abstract only]
	Schiffman R., et al. Migalastat improves gastrointestinal symptoms in patients with Fabry disease: Results from a double-blind, placebo-controlled phase 3 trial (FACETS)	<i>Journal of Inherited Metabolic Disease</i> , 2016, 39: S218. [Abstract only]
<b>Migalastat RCTs</b>		
ATTRACT and FACETS	Feldt-Rasmussen U, et al. Efficacy and safety of migalastat, an oral pharmacological chaperone for fabry disease: Results from two randomized phase 3 studies.	<i>Journal of Inherited Metabolic Disease</i> 2016, 39: S217. [Abstract only]
	Johnston FK., et al. Comparison of $\alpha$ -galactosidase A activity in white blood cells of patients (pts) with Fabry disease after 2 weeks of exposure to migalastat, agalsidase beta, or agalsidase alfa.	<i>Journal of Inherited Metabolic Disease</i> , 2016 39: S218. [Abstract only]
	Johnson, FK., et al. "Comparison of integrated white blood cell alpha-galactosidase a activity exposure between every-other-day orally administered migalastat and biweekly infusions of agalsidase beta or agalsidase alfa.	<i>Molecular Genetics and Metabolism</i> , 2016 117 (2): S63. [Abstract only]
	Hughes, D et al. Phenotype of Fabry disease in patients with mutations amenable to migalastat.	<i>Molecular Genetics and Metabolism</i> , 2016, 117 (2): S58-S59. [Abstract only]

Source: Table 6 pp24-25 of the submission.

6.5 The key features of the direct randomised trials are summarised in the table below.

**Table 2: Key features of the included evidence**

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

DB=double blind; MC=multi-centre; OL=open label; R=randomised.

Source: compiled during the evaluation

a Submission used mITT (amenable) population for primary analysis four patients were considered non-amenable post-hoc. The ITT population in ATTRACT consisted of 60 patients.

b Submission used mITT (amenable) population for primary analysis, 17 patients were considered non-amenable post-hoc. The ITT population consisted of 67 patients.

6.6 The overall risk of bias in ATTRACT and FACETS was high. Due to the small sample size and variability in the characteristics of the patient population, there is an increased risk of type II errors (such as would occur if the studies failed to detect an effect for migalastat even where one actually existed). The following issues were identified with regards to these trials:

- The efficacy results were based on the mITT (amenable) population, which was a post-hoc analysis. The sample size of the analyses conducted for both ATTRACT and FACETS was reduced due to the reclassification of GLA mutations for amenable patients and missing data were not imputed. The ESC noted that the impact of excluding these patients is unclear. In ATTRACT the use of the GLP-HEK assay changed the GLA mutation classification of 4 of the 60 patients from amenable to non-amenable. In FACETS, 17 of the 67 randomised patients were reclassified from amenable to non-amenable, and the proportion of patients with a GLA amenable mutations were not balanced across the treatment groups (migalastat 67% vs placebo 82%). The ESC noted that similar issues were raised in the publication in the New England Journal of Medicine.
- The variability in the baseline disease characteristics of the patients in the trials is widespread. It is not clear whether the severity criteria of Fabry-related organ burden in ATTRACT and FACETS is consistent with those used to enable patients to access ERT for Fabry disease in Australia. For instance, patients with clinically significant unstable cardiac disease including those with symptomatic arrhythmia were excluded from enrolling in ATTRACT. The extent of benefit patients would derive from treatment with migalastat in Australia is unclear. A higher proportion of patients with a less severe presentation would bias the results in favour of migalastat.
- Efficacy is defined in terms of intermediate outcomes, and collected over a short period of time. The results for ATTRACT and FACETS are for a maximum of 30 months of treatment.

- 6.7 Migalastat was considered to be non-inferior to ERT if the least squares (LS) mean annualised change in GFR for migalastat was no lower than 2.2 mL/min/1.73m<sup>2</sup>/year below the mean annualised rate of change for the ERT group, and the overlap in the 95% confidence intervals were more than 50%. This difference in GFR of 2.2 mL/min/1.73 m<sup>2</sup>/year is based on ATTRACT. The trial outcomes presented are biomarker surrogate outcomes, and there is likely to be a substantial time lag in detecting improvement after the onset of treatment. The longer-term implications of the intermediate outcomes such as the annualised change in GFR for organ function or survival are unknown. The submission did not address whether intermediate outcomes presented in ATTRACT and FACETS resulted in increased survival and/or improved quality of life.
- 6.8 The submission presented a supportive qualitative indirect comparison of migalastat and ERT using placebo as the common comparator in patients who are treatment naïve. Exchangeability was limited across the migalastat and ERT trials with respect to differences in trial eligibility criteria, gender, age, disease severity and time of conduct.
- 6.9 The duration of treatment in the clinical trials was relatively short (30 months), compared to the expected lifelong use of migalastat in clinical practice. The sponsor's PSCR stated that the treatment duration in the migalastat trials is no less than the evidence available for other Fabry disease therapies at registration. The ESC accepted that the 30 month treatment duration in the trials was reasonable.
- 6.10 The evaluation noted that it was unclear whether annualised change in GFR is a patient relevant endpoint and whether the non-inferiority criterion specified in the submission is acceptable. The sponsor's PSCR stated that GFR is a well-established predictor of cardiovascular disease and all-cause mortality. The ESC noted that that GFR is a biomarker surrogate outcome, but considered annualised change in GFR did indicate the treatment effect of migalastat and enzyme replacement therapy.
- 6.11 The ESC considered that it is not clear whether the severity of Fabry-related organ burden in the ATTRACT and FACETS trials is consistent with the established criteria for Fabry treatment in Australia. The PSCR stated that 88% and 92% of patients had at least two affected organs and associated low residual enzyme activity and elevated levels of plasma lyso-Gb3 in the ATTRACT and FACETS trials, respectively. This suggests that the majority of trial patients had severe Fabry disease and would meet the current eligibility criteria for treatment.

### ***Comparative effectiveness***

- 6.12 A summary of the comparative effectiveness of migalastat versus ERT (66% of patients were on agalsidase alfa and 34% were on agalsidase beta), and migalastat versus placebo, is presented in Table 3, Table 4 and Table 5. There were no statistically significant differences in any of the efficacy measures presented. These results should be interpreted with caution due to the small sample size of the clinical studies and post-hoc nature of the analyses.

- 6.13 The non-inferiority and comparability criteria proposed for the annualised rate of change in GFR were based on ATTRACT, which pre-specified that the difference between treatments were to be less than 2.2 mL/min/1.73m<sup>2</sup>/year, with more than a 50% overlap in the 95% CIs for both treatment groups. On the basis of the results presented in Table 3 the submission claimed that migalastat was non-inferior to ERT in the amenable population over the 18 month treatment period. The long-term implications of these results for renal function or survival are unclear.

**Table 3: Results of primary outcome in ATTRACT (Treatment experienced, 18 Months): annualised rate of change in GFR (mL/min/1.73m<sup>2</sup>/year)**

	Migalastat LS mean change (SE)	ERT LS mean change (SE)	Mean difference (95% CI)
<b>eGFR<sub>CKD-EPI</sub><sup>a</sup></b>			
ITT	-0.23 (1.12)	-2.85 (1.46)	2.62 (-0.99, 6.23)
mITT amenable <sup>c</sup>	-0.40 (0.93)	-1.03 (1.29)	0.63 (-2.49, 3.75)
<b>mGFR<sub>iohexol</sub><sup>b</sup></b>			
ITT	-4.29 (1.52)	-2.90 (1.98)	-1.39 (-6.28, 3.50)
mITT amenable <sup>c</sup>	-4.35 (1.64)	-3.24 (2.27)	-1.11 (-6.60, 4.38)

Abbreviations: CI, Confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ERT, Enzyme replacement therapy; GFR, Glomerular filtration rate; ITT, intention to treat; LS, least square; mITT, modified intention to treat; SE, standard error;

a eGFR<sub>CKD-EPI</sub>, glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

b mGFR<sub>iohexol</sub>, glomerular filtration rate measurement by iohexol clearance

c Amenable population is described in the submission as "ITT amenable" includes all randomised subjects with mutations amenable to GLP HEK assay. In FACETS, there were 6 subjects in the migalastat-migalastat group and 11 subjects in the placebo-migalastat group with non-amenable mutations (GLP HEK assay).

Source: Table 22 p52, Table 24 p55, Table 29 p60 of the submission; Table B.6.1 of the Commentary.

- 6.14 The 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. A post-hoc analysis of Stage 1 results was performed in the 50/67 patients with amenable mutations; 41% of migalastat and 28% of the placebo group achieved a response (relative risk: 1.44; 95% CI: 0.72, 2.89, see Table 4). The primary outcome was not met in the ITT population (p=0.30) and a responder analysis was not conducted for the amenable population. The benefit treatment naïve patients with Fabry disease would receive from migalastat is unclear.

**Table 4: Results of primary outcome in FACETS (Treatment naïve, 6 Months): kidney IC GL3 inclusions (ITT population)**

	Migalastat (N=34)	Placebo (N=33)
Responder: ≥50% reduction in kidney IC GL-3 inclusions, n (%)	13/32 <sup>a</sup> (40.6)	9/32 <sup>b</sup> (28.1)
Mean difference (95% CI)	12.5 (-13.4, 37.3), p=0.30	
Relative risk (95% CI)	1.44 (0.72, 2.89); p=NS <sup>c</sup>	

Abbreviations: CI, confidence interval; GL3, globotriaosylceramide; IC, interstitial capillaries; ITT: intention to treat; RR, relative risk

a 2 females missing from ITT population due to missing biopsy

b 1 patient missing from ITT population due to missing biopsy

c Calculated post hoc using RevMan 5.3

Source: Table 28 p60 of the submission: Table B.6.2 of the Commentary.

- 6.15 The submission claimed that migalastat was superior to ERT in reducing left ventricular mass index (LVMI) in Fabry patients. The claim of superiority was based

on migalastat achieving a greater reduction from baseline in LVMI compared with ERT in the mITT amenable population of ATTRACT. However, the mean difference in LVMI between the migalastat group and ERT group was not statistically significant (mean difference:  $-4.60 \text{ g/m}^2$ ; 95% CI:  $-4.77, 13.97$ ). The superiority claim thus depended on the within treatment group changes from baseline; for the migalastat group there was a mean change of  $-6.6 \text{ g/m}^2$ ; 95% CI:  $-11.01, -2.15$  and for ERT  $-2.0 \text{ g/m}^2$ , 95%CI:  $-10.99, 6.96$ . A subgroup analysis was also presented for the change in LVMI in patients with left ventricular hypertrophy (LVH) at baseline. The sample size for patients with LVH at baseline was further reduced from the overall sample, and, based on the available data, it was unclear if treatment with migalastat resulted in a reduction in LVMI in patients with LVH at baseline compared with those in the mITT amenable population

- 6.16 The same caveats pertaining to study interpretation (i.e. small sample size) apply in the interpretation of change in LVMI. The PBAC has previously considered that the clinical relevance of left ventricular mass as an outcome in Fabry patients was uncertain as these patients tend to suffer poor diastolic function (agalsidase alfa and agalsidase beta, November 2009 PSD p7).

**Table 5: Results of secondary outcome in ATTRACT and FACETS: Change in LVMI from baseline**

Study ID	ATTRACT [Treatment experienced]					FACETS [Treatment naïve]			
	18 months				30 Month	6 months		18 months	
	MIG N=36	ERT N=24	MIG N=36	ERT N=24	MIG-MIG N=31	MIG N=34	PBO N=33	OLE: MIG-MIG PBO-MIG	
Analysis group	mITT amenable		Subgroup: LVH b/line		OLE	mITT amenable		OLE	Subgroup : LVH b/line
LVMI ( $\text{g/m}^2$ )	n=34	n=13	n=13	n=5	n=28	n=25	n=16	n=27	n=8
Mean change (SD)	-6.6 (12.08)	-2.0 (14.86)	-8.4 (10.67)	4.5 (20.45)	-4.58 (13.15)	0.79 (8.15)	-1.46 (6.59)	-7.7 (3.7)	-18.6 (8.3)
95% CI	-11.01, -2.15	-10.99, 6.96	-15.69, 2.56	-10.71, 18.43	-8.87, 1.33	NR	NR	-15.4, -0.01 (p<0.05)	-38.2, 1.0 (p=NS)
Mean diff (95% CI)	-4.60 (-13.97, 4.77) p=NS		-12.90 (-31.99, 6.19) p=NS		NR	NR		NR	

Abbreviations: CI, confidence interval; ERT, Enzyme replacement therapy; LVH, Left ventricular hypertrophy; LVMI, left ventricular mass index; MIG, migalastat; N, number; NR, not reported; NS, not significant; OLE, open label extension; PBO, placebo; SD, standard deviation.

Text in italics was added or corrected as part of the evaluation. Mean differences were calculated post hoc.

Source: Table 24 p55, Table 30 p53 of the submission: *Table B.6.2 of the Commentary.*

### Comparative harms

- 6.17 The submission presented a summary of safety of all patients that received migalastat. A summary of safety outcomes for ATTRACT and FACETS is presented in Table 6.

**Table 6: Summary of adverse events (AEs) across the direct randomised trials – ATTRACT and FACETS**

Study ID	ATTRACT [Treatment experienced]			FACETS [Treatment naive]			
	18 months		30 Month	6 months		Stage 2 <sup>a</sup>	OLE period <sup>a</sup>
	MIG N=36	ERT N=24	MIG-MIG N=31	MIG N=34	PBO N=33	MIG-MIG/ PBO-MIG N=63	MIG-MIG/ PBO-MIG N=57
Summary of AEs							
Safety Population subjects, n	36	21	51	34	33	63	57
TEAEs (number of events)	308	166	598	204	142	240	242
TEAEs, subjects, n (%)	34 (94)	20 (95)	50 (98)	31 (91)	30 (91)	50 (79)	48 (84)
Related TEAEs, subjects, n (%)	14 (39)	3 (14)	19 (37) <sup>b</sup>	15 (44)	9 (27)	12 (19)	12 (21)
Severe TEAEs, subjects, n (%)	3 (8)	2 (10)	9 (18)	3 (9)	2 (6)	6 (10)	7 (12)
Treatment-Emergent SAEs, subjects, n (%)	7 (19)	7 (33)	16 (31)	2 (6)	4 (12)	5 (8)	11 (19)
Discontinued due to TEAEs, subjects, n (%)	0	0	0	0	1 (3)	1 (2)	0
AEs Leading to Death, subjects, n (%)	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; ERT, Enzyme replacement therapy; MIG, migalastat; OLE, Open label extension; PBO, placebo; SAE, Serious adverse event; TEAE, Treatment-emergent adverse events;

<sup>a</sup> The overall summary of TEAEs is reported by treatment period for FACETS. i.e. the OLE does not include AEs that occurred during Stage 1 or Stage 2 of FACETS. Data is reported as an aggregated total both treatment groups MIG-MIG and PBO-MIG.

Source: Table 36 p68, Table 40 p74 of the submission: Table B.6.3 of the Commentary.

- 6.18 The most commonly reported treatment emergent adverse events (TEAEs) in ATTRACT after 18 months were nasopharyngitis (both migalastat and ERT 33%) and headache (migalastat 25%; ERT 24%). Dizziness (17%), abdominal pain (14%), diarrhoea (14%) and nausea (14%) were more frequently seen in the migalastat group than in the ERT group. TEAEs more frequently observed in the ERT group compared to migalastat included: influenza (19% vs 14%), cough (24% vs 8%), back pain (14% vs 11%), bronchitis (14% vs 6%), vomiting (14% vs 8%) and sinusitis (14% vs 8%).
- 6.19 In FACETS, the AEs reported with a higher frequency in the migalastat group compared to placebo were headache and nasopharyngitis after 6 months.
- 6.20 The ESC noted that some of the commonly reported TEAEs in the migalastat group (dizziness, abdominal pain, diarrhoea and nausea) are also symptoms of Fabry disease.

### **Benefits/harms**

- 6.21 A summary of the comparative benefits and harms for migalastat versus ERT are presented in the Table 7 below.

**Table 7: Summary of comparative benefits and harms for migalastat and ERT/PBO**

Trial	Migalastat	ERT	PBO	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					Migalastat	ERT	PBO	
<b>Benefits</b>								
<b>Composite clinical outcome<sup>a</sup> at 18 months (mITT Amenable)</b>								
ATTRACT	10/34	8/18	-	0.66 (0.32, 1.38)	29.4	44.5	-	-15.0% (-42.6%, 12.6%)
<b>Patients with &gt;50% reduction in GL3 inclusions per kidney (ITT)</b>								
FACETS	13/32	-	9/32	1.44 (0.72, 2.89)	40.6	-	28.1	12.5% (-10.6%, 35.6%)
<b>Annualised rate of change in eGFR<sub>CKD-EPI</sub> (mL/min/1.73m<sup>2</sup>/year)</b>								
	Migalastat			ERT/placebo			Mean difference*: migalastat vs. ERT/placebo (95% CI)	
	n	Mean Δ baseline	SD	n	Mean Δ baseline	SD		
ATTRACT, ITT	36	-0.52	4.29	21	-3.00	9.88	2.62 (-0.99, 6.23)	
ATTRACT, mITT amenable	34	-0.63	4.30	18	-1.50	7.43	0.63 (-2.49, 3.75)	
FACETS	34	2.3	17.30	30	-1.2	14.37	3.50 (-4.26, 11.26)	
FACETS mITT amenable	28	0.3	17.05	20	2.0	15.36	-1.70 (-10.93, 7.53)	
<b>Harms</b>								
	Migalastat	ERT	PBO	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					Migalastat	ERT	PBO	
<b>Treatment emergent adverse event (TEAE)</b>								
ATTRACT	34/36	20/24	-	1.13 (0.93, 1.38)	94.4	83.3	-	11.1% (-5.6%, 27.8%)
FACETS	31/34	-	30/33	1.00 (0.86, 1.17)	91.2	-	90.9	0.3% (-13.4%, 13.9%)
<b>Related TEAE</b>								
ATTRACT	14/36	3/24	-	3.11 (1.00, 9.68)	38.9	12.5	-	26.4% (5.7%, 47.1%)
FACETS	15/34	-	9/33	1.62 (0.82, 3.17)	44.1	-	27.3	16.8% (-5.7%, 39.4%)
<b>Severe TEAE</b>								
ATTRACT	3/36	2/24	-	1.00 (0.18, 5.55)	8.3	8.3	-	0.0% (-14.3%, 14.3%)
FACETS	3/34	-	2/33	1.46 (0.26, 8.16)	8.8	-	6.1	2.8% (-9.8%, 15.3%)

<sup>a</sup> Composite clinical outcome: Renal events were classified subsequent to a decrease in eGFR<sub>CKD-EPI</sub> ≥15 mL/min/1.73m<sup>2</sup> with decrease in eGFR <90 mL/min/1.73m<sup>2</sup> from baseline, or an increase in 24-hour urine protein ≥ 33% with increased protein ≥ 300 mg, from baseline. These definitions represent episodes of acute renal injury in patients with underlying renal disease; Cardiac events included myocardial infarction; unstable angina; new symptomatic arrhythmia requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; or congestive heart failure; Cerebrovascular events included transient ischaemic attack (TIA) and stroke.

\*Duration of follow-up: ATTRACT= 18 months; FACETS = 6 months;

Abbreviations: CI, Confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ERT, Enzyme replacement therapy; GFR, Glomerular filtration rate; GL3, globotriaosylceramide; ITT, intention to treat; mITT, modified intention to treat; PBO, placebo; RD, risk difference; RR, risk ratio; SD, standard deviation; TEAE, Treatment-emergent adverse events; Source: Compiled during the evaluation, Table 22 p52, Table 24 p55, Table 29 p60 of the submission; Table B.6.1 of the Commentary.

### **Clinical claim**

- 6.22 The submission described migalastat as non-inferior in terms of comparative effectiveness and safety over the primary comparator, ERT, in patients with Fabry disease aged 16 years and older with an amenable mutation. The claim is based on biomarker surrogate outcomes. The long-term implications of the intermediate outcomes of the annualised change in GFR on long term organ function or survival is unknown. The claim of non-inferiority is reasonable for treatment experienced or switch patients, based on the annualised change in eGFR based results in ATTRACT and the submission's proposed non-inferiority criteria. The mean difference in  $eGFR_{CKD-EPI}$  between migalastat and ERT in the mITT amenable population was 0.63 mL/min/1.73m<sup>2</sup>/year. However, analyses of the trials were based on the amenable population, which reduced the sample sizes of the analyses conducted. These analyses were post-hoc in nature and the trials were not powered to detect differences in the outcomes.
- 6.23 The submission's claim of non-inferiority of efficacy and safety of migalastat to ERT was not adequately supported in the treatment-naïve population. FACETS was a placebo controlled trial and did not provide comparative evidence with ERT. The statistical power of the study was substantially reduced in the analysis of the amenable population. The extent of benefit to treatment-naïve patients with Fabry disease who are treated with migalastat is unclear. The submission presented a supportive qualitative indirect comparison of migalastat and ERT using placebo as the common comparator in support of this claim. However, no comparative evidence was provided for migalastat and agalsidase beta, and qualitative comparisons of efficacy with agalsidase alfa were limited in terms of the exchangeability of the included trials. The ESC considered while migalastat may provide a small benefit compared to placebo in treatment-naïve patients, the comparative efficacy against the comparators has not been established. The ESC noted, in regards to subsidy of migalastat only in treatment-experienced patients, that the PSCR stated there is a likelihood that treatment naïve patients who wish to use migalastat will use ERT in order to gain eligibility, leading to the same outcome in a less efficient manner. Further, the PSCR claimed the submission shows that there will be one new patient seeking subsidy for treatment per year (including amenable and non-amenable patients). The ESC considered that this claim may be an underestimate in practice.
- 6.24 The claim for non-inferiority of safety may be reasonable. However, the TGA assessment of ATTRACT and FACETS is ongoing, and advice of this assessment is expected to be available after the March 2017 PBAC meeting.

### **Economic analysis**

- 6.25 The equi-effective doses are estimated as migalastat 150 mg every other day, and agalsidase alfa 0.2 mg/kg and agalsidase beta 1.0 mg/kg fortnightly. This was based on the product information doses for the two products as indicative of likely clinical practice. Information on the mean doses of agalsidase alfa and agalsidase beta dosing was not reported from ATTRACT (the comparative study). It was thus not possible to estimate trial based equi-effective doses for migalastat with ERT. This resulted in uncertainty in the equi-effective dose. The PSCR reiterated that the study required patients to be on the full labelled dose of ERT prior to enrolment and during the study. The PSRC argued the deviations from the expected utilisation thus reflect variations in compliance. The mean and median compliance was high across both

the migalastat and ERT groups (mean: 99.07%; median: 99.82% and mean: 97.03%; median: 100%) respectively. While the actual doses were not reported in the ATTRACT trial, the ESC accepted that the proposed methodology to derive the equi-effective doses was reasonable.

- 6.26 Based on the methodology in the submission, the annual cost of treatment per patient differs between all three treatments. Agalsidase beta was estimated to be \$ [REDACTED] per patient per year, compared to agalsidase alfa at \$ [REDACTED] per patient per year. Migalastat is estimated to be \$ [REDACTED] per patient per year.
- 6.27 No additional costs/offsets for initiation on to migalastat or monitoring of adverse events as requested in the draft PI were included. The cost of the Galafold GLP-HEK assay test was not included in the cost-minimisation analysis. The submission stated 'Amicus Therapeutics will test the novel mutation for amenability using the Galafold Amenability Assay at no cost to the patient or healthcare system'. According to the PSCR, while the assay and blood collection costs will be borne by the sponsor, patients with novel GLA mutations will require a single further appointment with their treating physician, at a total cost of \$528.40 to the MBS over the first five years of listing. The sponsor also proposed to cover additional costs of monitoring patients for adverse events. The ESC noted that as these procedures would occur in different health care settings, it could be complicated to implement an agreement between all stakeholders. An alternative could be to include these costs as an offset in the cost-minimisation analysis against the comparators.

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

- 6.28 The submission used the annual cost per patient calculated as the weighted average of annual ERT use which was \$ [REDACTED]. The relative market shares of agalsidase alfa and agalsidase beta used to calculate the cost-minimised price were 37.5% and 62.5%, respectively. There is uncertainty regarding these market shares for agalsidase alfa and agalsidase beta which affects their applicability in estimating the cost-minimised price for migalastat. According to the PSCR, the market shares were derived from the LSDP review (2014) based on Fabry patients currently receiving treatment in Australia. The prior use of ERT at baseline in the ATTRACT trial for migalastat patients was 67% (24) agalsidase alfa and 31% (11) agalsidase beta; and for ERT patients it was 62% (13) agalsidase alfa and 38% (8) agalsidase beta. These shares are the inverse of those used in the estimation of the cost-minimisation analysis. Given the difference in cost of the ERT products, the cost per patient per year for migalastat would be lower (\$ [REDACTED]) if calculated using the proportions of use of ERT products from ATTRACT.
- 6.29 The submission did not present the cost per script. However, this was estimated during the evaluation at \$ [REDACTED] per pack (14 capsules) which is \$ [REDACTED] per prescription for 16 weeks of treatment (initial plus 3 repeats for 4 packs in total). The annual cost is \$98,963 per script multiplied by 3.26 scripts (365 days/7 days weeks/16 weeks), equating to \$ [REDACTED] per year. In the PSCR, the sponsor agreed to increase the number of repeats to allow 24 weeks of treatment, consistent with current practice for ERTs.

**Estimated PBS usage & financial implications**

6.30 This submission was not considered by DUSC. The submission presented a mixed epidemiological/market share approach to forecast the uptake and cost of migalastat over a five year period. The submission calculated the total number of migalastat eligible patients by multiplying the amenability proportion (45%) by the █ patients currently receiving ERT and the █ 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 █ grandfathered patients in Year 1, which underestimated the uptake by new patients.

**Table 8: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number eligible	█	█	█	█	█
Market share	30%	40%	50%	60%	60%
Number patients receiving migalastat	█	█	█	█	█
Scripts <sup>a</sup>	█	█	█	█	█
<b>Estimated net cost to Government budget</b>					
Net cost to Government	█	█	█	█	█
Net cost offsets to Government from ERT substitution	█	█	█	█	█
Net cost to Government – corrected patient numbers	█	█	█	█	█
Net cost offsets to Government from ERT substitution – corrected patient numbers	█	█	█	█	█
<b>Estimated total net cost</b>					
Net cost to Government	\$0	\$0	\$0	\$0	\$0

<sup>a</sup>Number of scripts per year calculated as 3.259 per year (365/7)/16 weeks) during the evaluation. Correction for patient numbers as the submission calculated the total number of migalastat eligible patients by applying the amenability proportion (45%) to the █ patients currently receiving ERT and the █ 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 6 grandfathered patients in Year 1, thus underestimating the uptake by new patients

Source: Source: Table 71, p.128 of the submission Excel spreadsheet 'migalastat\_Section E\_Nov16\_PBAC', and calculated during the evaluation

6.31 The submission assumed that the increased cost of funding migalastat will be equal to the reduced market share of the two ERTs (agalsidase alfa and agalsidase beta). At Year 5, the estimated number of patients was approximately 21 and the net cost to Government was \$0.

6.32 There is uncertainty around the patient numbers, in particular around the proportion of amenable patients and market share. Neither of these is likely to impact on the net cost of the PBS based on the cost-neutrality of the proposed price.

6.33 The submission stated that the cost of the GLP-HEK assay to determine eligibility for migalastat will not be borne by the patient. The submission did not present any details of how patients or the health care system would be reimbursed for any costs that might be incurred in determining migalastat amenability. The ESC noted that the sponsor in the PSCR, proposed that costs of the assay, blood collection and monitoring patients for adverse events will be borne by the sponsor and indicated that there would be an additional cost to the MBS (discussed above in the Economic Analysis section).

- 6.34 Further the ESC noted that the number of eligible patients seeking treatment for Fabry disease (either with ERT or migalastat) may increase significantly as late onset disease is recognised and diagnosed. When late onset variants are considered, the prevalence of Fabry disease increases from 1:80,000 live births to 1:3000 (Orphanet website, Orpha number 324). The increased cost to Government is unknown. The pre-PBAC response acknowledged that the prevalent number of Fabry diagnoses in Australia may increase due to improved diagnosis of late onset disease. However, it was noted that in the absence of migalastat, patients found to be eligible for treatment through the LSDP would be treated with ERT and migalastat itself is not expected to result in an increase in the size of the patient population.

### **Quality Use of Medicines**

- 6.35 The submission presented the risk minimisation materials for patients to support the quality use of migalastat and compliance in people with Fabry disease. This included personalised advice, support and information through a smartphone application, and visits from the sponsor's nurse.

### **Financial Management – Risk Sharing Arrangements**

- 6.36 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.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred making a recommendation on the listing of migalastat for Fabry Disease pending the outcome of the TGA evaluation.
- 7.2 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 for the reasons outlined by the ESC.
- 7.3 The PBAC noted that the clinical evidence in the submission was one head-to-head trial (ATTRACT) comparing migalastat to ERT in treatment-experienced patients, and one head-to-head trial (FACETS) comparing migalastat to placebo in treatment-naïve patients. Noting the concerns of the evaluation and the ESC, the PBAC recognised that Fabry disease is a rare condition leading to difficulties undertaking clinical trials in this patient population.
- 7.4 The outcome of the ATTRACT trial was annualised change in GFR. While GFR is a biomarker surrogate outcome, PBAC agreed with ESC and considered annualised change in GFR was a reliable marker of long-term kidney outcome. The submission claimed that the criterion for migalastat to be considered non-inferior to ERT was the least squares (LS) mean annualised change in GFR for migalastat was no lower than  $2.2 \text{ mL/min}/1.73\text{m}^2/\text{year}$  below the mean annualised rate of change for the ERT

group, and the overlap in the 95% confidence intervals was more than 50%. The PBAC considered that the non-inferiority criterion had not been fully justified. 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.

- 7.5 Further, 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. The PBAC recalled that it has previously considered the clinical relevance of left ventricular mass as an outcome in Fabry patients to be uncertain.
- 7.6 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.
- 7.7 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. Therefore, the PBAC could not accept the clinical claim of comparative effectiveness over the primary comparator, ERT in treatment naïve patients and in treatment experienced or switch patients.
- 7.8 The submission claimed that migalastat was non-inferior in terms of comparative safety over the primary comparator, ERT. The PBAC noted that the FACETS trial was placebo controlled and that there was no formal indirect comparison of safety comparing migalastat to ERTs in the supportive analysis in treatment naïve patients. 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.
- 7.9 The pre-PBAC response reiterated the advantages of migalastat, an oral treatment over ERT. The PBAC noted that the submission had not formally addressed any associated benefits to patients using migalastat rather than ERT.
- 7.10 The PBAC noted that determining the eligibility of patients for migalastat was not straightforward, and the evidence base for this determination is evolving. The principle is that only patients with an amenable mutation in the sequenced GLA gene would benefit from being treated with migalastat. The Galafold Amenable Table (GAT), used to determine if a mutation is amenable, is based on the results of a GLP-HEK assay which was validated during the conduct of the key trial (Benjamin et al, 2016, Genetics in Medicine). These data were the used to generate a post hoc analysis of this trial excluding some patients who were determined to have amenable mutations based on a preliminary GLP-HEK assay, but were determined not to be amenable with the later 'validated' assay. The PBAC raised concerns about the extent to which the performance of the assay is operator-dependent, which could affect the number of eligible patients and their average response to therapy. The PBAC raised concerns about [REDACTED] the performance of the assay [REDACTED]. The GAT is further updated when the amenability

status of a previously untested GLA mutation is unknown and thus needs to be tested using the validated GLP-HEK assay. The pre-PBAC response clarified that the assay uses a synthetic copy of the previously untested GLA mutation based on the known genetic sequence (as identified through the routine sequencing to confirm a genetic diagnosis of Fabry disease) and not material from the sample of the patient which identified the previously untested GLA mutation. The PBAC noted that the GLA mutation sequence is determined by current standard genetic sequencing procedures. Overall, 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 GAT, has not been assessed in the context of Australian standard genetic testing. 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. The PBAC noted that public subsidy of the validated GLP-HEK assay has not been requested by the sponsor, but would be implicit by virtue of any public subsidy for the medicine.

- 7.11 The PBAC considered a cost-minimisation analysis to be an appropriate approach to the 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 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.
- 7.12 The submission claimed that there would be zero net cost to Government by subsidising migalastat. The PBAC noted that the cost of migalastat was different to the agalsidase alfa and agalsidase beta and was related to the assumed market share of ERTs. If the actual market share between agalsidase alfa and agalsidase beta in one year differed to this assumed market share, then reduction in the total cost of ERT may not be equal to the cost of migalastat. In addition, while the draft product information of migalastat states 'Not intended for concomitant use with ERT', the PBAC noted that positive outcome Warnock et al, Oral Migalastat of the proof of concept study in patients by HCl Leads to Greater Systemic Exposure and Tissue Levels of Active  $\alpha$ -Galactosidase A in Fabry Patients when Co-Administered with Infused Agalsidase. PLoS O.NE. 2015 10(8): e0134341. 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 actions, and that migalastat may be used after 'failure' of ERT. The PBAC considered that the claims of cost-neutrality are therefore questionable.
- 7.13 The PBAC considered further information from the sponsor would be required to address the PBAC's concerns for this deferred submission. As well as providing an update on the TGA's evaluation of migalastat and addressing the concerns of the ESC and PBAC, the sponsor should provide additional evidence of the clinical benefit of migalastat. 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).

- 7.14 The PBAC noted that this submission is not eligible for an Independent Review, as it has not been rejected.

**Outcome:**

Deferred

**8 Context for Decision**

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

**9 Sponsor's Comment**

Amicus are not in agreement with some of PBAC's conclusions on migalastat. We believe migalastat is safe and effective relative to the infused ERT and are committed to ensuring Australian patients have access to this innovative oral treatment. We believe that the outstanding concerns highlighted by the PBAC have been addressed in a minor submission that was lodged in April this year.