PUBLIC SUMMMARY DOCUMENT

Topic: Updated literature review of agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®) for the treatment of Fabry disease

Sponsors: Shire Australia Pty Ltd and Genzyme Australasia Pty Ltd

Date of PBAC Consideration: November 2009

1. Purpose of Item

The PBAC was to consider a report on the updated literature review of the comparative efficacy and safety of agalsidase alfa (Replagal®) versus agalsidase beta (Fabrazyme®) supplied under the Life Saving Drugs Program (LSDP) for the treatment of Fabry disease, to determine whether the pricing disparity in the average yearly patient treatment cost at the registered doses between these agents was justified.

2. Background

Agalsidase alfa and agalsidase beta were added to the LSDP in 2004.

In January 2009, the Access and Systems Branch of the Department of Health and Ageing requested the PBAC's advice on the current drugs (agalsidase alfa and agalsidase beta) used to treat Fabry disease under the LSDP. A literature review was conducted in February 2009 to update the evidence base for both agalsidase alfa and beta (previously reviewed by the PBAC in 2002-2003) as well as to evaluate the comparative efficacy and safety of the two treatments. Both sponsors were given the opportunity to prepare detailed submissions for the November 2009 PBAC meeting. The purpose of this current review was to evaluate the new data presented in these submissions and to identify any issues related to the comparative efficacy and safety of the two treatments. This current review was supplementary to the original review conducted in February 2009.

3. Registration Status

Agalsidase alfa (ghu) was registered with the Therapeutic Goods Administration (TGA) on 17 May 2002 for long-term enzyme replacement therapy of patients with Fabry disease (alpha-galactosidase A deficiency).

Agalsidase beta-rch was TGA registered on 30 May 2002 for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (alpha-galactosidase deficiency).

4. Clinical Place for the Proposed Therapy

Fabry disease is a rare (incidence generally estimated at 1 in 40,000 to 1 in 117,000), X-linked genetic disorder caused by a deficiency of the enzyme alpha-galactosidase A, which is required for the degradation of globotriaosylceramide (GB3 or GL-3) and other related glycosphingolipids. Accumulation of glycosphingolipids in various tissues (particularly the kidneys, heart and brain) of patients with Fabry disease can disrupt cellular function and lead to the development of serious complications and reduced life expectancy. Treatment with either agalsidase alfa or agalsidase beta provides an exogenous source of the alpha-galactosidase A enzyme.

5. Clinical Trials

The scientific basis of the February 2009 report was one head-to-head trial of agalsidase alfa versus agalsidase beta (Vedder et al 2007), two trials of agalsidase alfa versus placebo (Schiffmann et al 2001, Hajioff et al 2003) and two trials of agalsidase beta

versus placebo (Eng et al 2001, Banikazemi et al 2007). These studies are shown below. Various extensions of these trials provided data beyond the initial trial periods.

Trial/First author	Protocol title	Publication citation
Direct randomised trials: agalsidase alfa vs. agalsidase beta		
Vedder et al. (2007)	Treatment of Fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg.	*PLoS One* 2(7): e598
Placebo randomised trials of agalsidase alfa (& extensions)		
Schiffmann et al. (2001)	Enzyme Replacement Therapy in Fabry Disease: A Randomized Controlled Trial.	*Journal of the American Medical Association* 285:2743-2749
	Regional Cerebral Hyperperfusion and Nitric Oxide Pathway Dysregulation in Fabry Disease: Reversal by Enzyme Replacement Therapy.	*Circulation* 104:1506-1512
	Elevated Cerebral Blood Flow Velocities in Fabry Disease With Reversal After Enzyme Replacement.	*Stroke* 33: 525-531
	Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease.	*BMC Neurology* 2:4
	Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease.	*Muscle & Nerve* 28:703-710
	Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting.	*Nephrology, Dialysis, Transplantation* 21: 345-354
	Enzyme Replacement Therapy and Intraepidermal Innervation Density in Fabry Disease.	*Muscle & Nerve* 34: 53-56
Hajioff et al. (2003)	Hearing loss in Fabry disease: The effect of agalsidase alfa replacement therapy.	*Journal of Inherited Metabolic Diseases* 26: 787-794
	Hearing improvement in patients with Fabry disease treated with agalsidase alfa.	*Acta Paediatrica* Supplement 443: 28-30
Hughes et al. (2008)	Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa.	*Heart* 94: 153-158
Placebo randomised trials of agalsidase beta (& extensions)		
Eng et al. (2001)	Safety and Efficacy of Recombinant Human alpha-galactosidase A Replacement Therapy in Fabry's Disease.	*New England Journal of Medicine* 345: 9-16
	Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy.	*Kidney International* 62: 1933-1946
	Monitoring the 3-Year Efficacy of Enzyme Replacement Therapy in Fabry Disease by Repeated Skin Biopsies.	*Journal of Investigative Dermatology* 122:900-908
	Long-Term Safety and Efficacy of Enzyme Replacement Therapy for Fabry Disease.	*American Journal of Human Genetics* 75: 65-74
	Sustained Long-Term Renal Stabilization After 54 Months of Agalsidase Beta Therapy in Patients with Fabry Disease.	*Journal of the American Society of Nephrology* 18: 1547-1557
Bierer et al. (2006)	Improvement in serial cardiopulmonary exercise testing following enzyme replacement therapy in Fabry disease.	*Journal of Inherited Metabolic Disease* 29(4):572–579.
Banikazemi et al. (2007)	Agalsidase-Beta Therapy for Advanced Fabry Disease: A Randomized Trial.	*Annals of Internal Medicine* 146:77-86

The Bierer et al (2006) randomised controlled trial was excluded from the review due to insufficient sample size (6 patients randomised, 4 received agalsidase beta and 2 received placebo).

New supportive studies related to the efficacy and safety of agalsidase alfa and agalsidase beta were identified by each of the sponsors and are shown in the table below. Included studies identified in the submissions are grouped according to the main research aim of each study.

Trial ID/First author	Protocol title	Publication citation
Dose ranging studies & studies using non-approved doses		
Clarke et al. (2007)	The pharmacology of multiple regimens of agalsidase alfa enzyme replacement therapy for Fabry disease.	*Genetics in Medicine* 9: 504-509
Eng et al. (2001b)	A phase 1/2 clinical trial of enzyme replacement in Fabry disease: Pharmacokinetic, substrate clearance and safety studies.	*The American Journal of Human Genetics* 68: 711-722
Lubanda et al. (2009)	Evaluation of a low dose, after a standard therapeutic dose, of agalsidase beta during enzyme replacement therapy in patients with Fabry disease.	*Genetics in Medicine* 11: 256-264
Schiffmann et al. (2007)	Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing.	*Journal of the American Society of Nephrology* 18: 1576-1583
Renal outcome studies		
Cybulla et al. (2009)	Kidney transplantation in patients with Fabry disease.	*Transplant International* 22: 475-481
Feriozzi et al. (2009)	Agalsidase alfa slows the decline in renal function in patients with Fabry disease.	*American Journal of Nephrology* 29: 353-361
West et al. (2009)	Agalsidase alfa and kidney dysfunction in Fabry disease.	*Journal of the American Society of Nephrology* 20: 1132-1139
Cardiovascular outcome studies		
Beer et al. (2006)	Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy.	*The American Journal of Cardiology* 97: 1515-1518
Imbriaco et al. (2009)	Effects of enzyme-replacement therapy in patients with Anderson-Fabry disease: a prospective long term cardiac magnetic resonance imaging study.	*Heart* 95: 1103-1107
Weidemann et al. (2003)	Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: A prospective strain rate imaging study.	*Circulation* 108: 1299-1301
Weidemann et al. (2009)	Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: Evidence for a better outcome with early treatment.	*Circulation* 119: 524-529
Women and children studies		
Baehner et al. (2003)	Enzyme replacement therapy in heterozygous females with Fabry disease: Results of a phase IIIB study.	*Journal of Inherited Metabolic Disease* 26: 617-627
Schiffmann et al. (2009)	Agalsidase alfa in children with Fabry disease – A 4-year prospective study.	*Abstract presented at American College of Medical Genetics Annual Meeting in March 2009*.
Whybra et al. (2009)	A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase	*Genetics in Medicine* 11: 441-449

Trial ID/First author	Protocol title	Publication citation
	alfa in 36 women with Fabry disease.	
Immunogenicity studies		
Benichou et al. (2009)	A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease.	*Molecular Genetics and Metabolism* 96:4-12
Linthorst et al. (2004)	Enzyme therapy for Fabry disease: Neutralizing antibodies toward agalsidase alpha and beta.	*Kidney International* 66: 1589-1595
Vedder et al. (2008)	Treatment of Fabry disease with different dosing regimens of agalsidase: Effects on antibody formation and GL-3.	*Molecular Genetics and Metabolism* 94: 319-325

At the time of the February 2009 literature review there were no published randomised trials that directly compared the efficacy of agalsidase alfa and agalsidase beta at currently approved doses (alfa 0.2 mg/kg every other week; beta 1.0 mg/kg every other week).

6. Results of Trials

In general, 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). In the only head-to-head trial, agalsidase alfa and beta appeared to have similar short-term efficacy (24 months) at an equal dose of 0.2 mg/kg every other week (no differences in reported clinical or surrogate endpoints with neither product achieving the primary endpoint at 0.2 mg/kg). However it was difficult to make comparisons between agalsidase alfa and beta in the placebo controlled trials due to the differences in patient populations and outcome measures.

Biochemical / pharmacokinetic evidence:

The PBAC noted that the amino acid sequences of both products are identical. In terms of glycosylation, the oligosaccharide side chains are similar in both products, however there are some slight differences, namely that agalsidase beta (which is produced from cultured CHO cell lines) has a higher proportion of mannose-6-p (which is required for binding to target cells and delivery to the lysosome) compared to agalsidase alfa which carries the same glycosylation profile as the native human enzyme. The differences in glycosylation are summarised in the table below, taken from Lee et al (2003).

Table III. Monosaccharide composition

Monosaccharide	Monosaccharide mol/mol protein	
	Fabrazyme	Replagal
Fucose	1.8 ± 0.1	3.0 ± 0.3
Galactose	8.0 ± 0.4	12.2 ± 1.0
N-acetylglucosamine	18.4 ± 0.8	22.5 ± 2.3
Mannose	25.7 ± 1.8	27.6 ± 0.5
Mannose-6-phosphate	3.1 ± 0.1	1.8 ± 0.0
N-acetylneuraminic acid	7.0 ± 1.0	6.9 ± 0.6
Sialic acid:galactose	0.88	0.56

Source: Lee et al, *Glycobiology* 2003; 13 305

The PBAC noted that the pharmacokinetic characteristics of the products are also similar, with receptor binding improved in agalsidase beta compared to agalsidase alfa, but no difference in fibroblast uptake at 10 hours after dosing. It was also noted that Blom et al (2003) showed that functional correction of Fabry fibroblasts in vitro for both products was also identical at identical molar exposure (0.1 mmol per hour for 3 hours).

The registered doses of the agalsidase treatments reflected the dosage used in the trials.

Overall, the PBAC agreed that there is neither biochemical nor pharmacokinetic evidence to explain the five-fold difference in dose (alfa 0.2 mg/kg every other week versus beta 1.0 mg/kg every other week) between the products.

Dose-ranging studies

The PBAC considered that overall, many of the dose-ranging studies included in the submissions were inadequate to determine the optimal dose, since they were all short term studies. All studies used plasma GB3 levels as their primary endpoint. Eng et al (2001b) suggested faster plasma GB3 clearance at higher doses and GB3 was effectively cleared from endothelium of the liver, skin, heart and kidney with agalsidase beta. For agalsidase alfa, no differences were shown between 0.2 mg/kg biweekly and higher doses (including 0.4 mg/kg biweekly, 0.2 mg/kg weekly and 0.4 mg/kg weekly) in a 10 week study to evaluate the effect of dose and dosing frequency on plasma GB3 levels (Clarke et al (2007).

Two longer term (24 months) studies investigating non-approved dosage regimens were also presented. The PBAC noted Shiffmann et al (2007) compared agalsidase alfa 0.2 mg/kg at dosing frequencies of biweekly (2-4 years) then weekly (further 2 years) and found no changes in plasma or urine GB3 beyond the significantly reduced levels already observed with biweekly dosing. A reduced rate of decline in estimated glomerular filtration rate (eGFR) was observed, with increased dose frequency in this group of patients. The PBAC also noted Lubanda et al (2009) reported that the majority of patients switched to a lower maintenance dose of agalsidase beta (0.3 mg/kg every other week) after being treated with the standard dose of agalsidase beta (1.0 mg/kg every other week for 6 months) maintained similar levels of GB3 clearance, thereby noting that a lower

maintenance dose may be sufficient for some patients after stabilisation with the standard dosing. However Lubanda et al (2009) note that the long term clinical effects of transitioning to the lower dose have not been evaluated.

Clinical outcome studies

The PBAC noted that there were no published randomised controlled trials comparing agalsidase alfa and agalsidase beta at their approved doses. The only published head-to-head trial of agalsidase treatments compared both treatments at the same dose of 0.2 mg/kg every other week (Vedder et al 2007). The recommended dose of agalsidase beta is 1.0 mg/kg every other week.

Vedder et al (2007) showed no significant differences between treatments when agalsidase alfa and agalsidase beta were compared at identical doses of 0.2 mg/kg biweekly, as shown in the table below. High rates of treatment failure were noted by the authors in both treatment groups dosed at 0.2 mg/kg biweekly however it was also noted that treatment failure occurred predominantly in patients with more extensive pre-treatment manifestations based on the Mainz Severity Score Index scores and were generally older than non treatment failures.

Summary of results of the direct comparison between agalsidase alfa and agalsidase beta (Vedder et al 2007)

Outcome	n	Agalsidase alfa (0.2 mg/kg) [N = 20]	n	Agalsidase beta (0.2 mg/kg) [N = 16]
Primary outcome				
LV mass	13	Baseline median 288g (range 177, 479)	13	Baseline median 316g (range 213, 517)
	10	Median change at 12 months -23g (range -167, 136) $p = 0.51$	10	Median change at 12 months -46g (range -226, 131) $p = 0.17$
	No significant change was observed in either treatment group at 12 months or 24 months (data not reported)			
Key secondary outcomes				
Treatment failure[a]	18	5 (28%) patients failed treatment within 24 months	16	3 (19%) patients failed treatment within 24 months
	The time to occurrence of treatment failure did not differ between treatment groups ($p = 0.54$)			
Urinary GL-3	NR	Median change at 12 months -284 nmol/24hr (range -4939, 1350), $p = 0.04$	NR	Median change at 12 months -265 nmol/24hr (range -1216, 1450, $p = 0.66$
	Agalsidase alfa significantly reduced urinary GL-3 compared to baseline. There was no significant difference in the median change at 12 months between alfa and beta ($p = 0.65$)			
Plasma GL-3	10	Median change at 12 months -2.56 umol/L (range -5.81, 0.32), $p = 0.009$	8	Median change at 12 months -1.84 umol/L (range -5.17, -0.23), $p = 0.012$
	Both treatments significantly reduced plasma GL-3 compared to baseline. There was no significant difference in the median change at 12 months between alfa and beta ($p = 0.46$)			

Abbreviations: LV, left ventricular

[a] Treatment failure was defined as progression of renal disease (33% increase in serum creatinine, need for dialysis or transplantation); cardiac disease (new infarction, need for cardioversion, or anti-arrhythmic drugs, heart-failure necessitating hospitalization), or occurrence of a new cerebrovascular accident as diagnosed by a neurologist or new lacunar infarctions on magnetic resonance imaging as assessed by an experienced neuro-radiologist.

For the primary outcome of change in left ventricular mass, no significant change was observed in either treatment group at 12 months or 24 months. The PBAC considered that the results of this trial were uncertain due to the small sample size, open label design and possible differences in patient discontinuations between the treatment arms.

Summary of clinical events in agalsidase beta trials

Trial ID	Outcome	Agalsidase	Placebo	Hazard ratio (95% CI)
Agalsidase beta vs. placebo				
Banikazemi (2007)	Time to first clinical event	Patients with clinical events 14/51 (27%)	Patients with clinical events 13/31 (42%)	0.47 (0.21, 1.03) (p = 0.06)[a]
	Time to first renal event	Patients with renal events 10/51 (20%)	Patients with renal events 7/31 (23%)	0.49 (0.17, 1.4) (p = 0.18)
	Time to first cardiac event	Patients with cardiac events 3/51 (6%)	Patients with cardiac events 4/31 (13%)	0.42 (0.058, 2.7) (p = 0.42)
	Time to first cerebrovascular event	Patients with cerebrovascular events 0/51 (0%)	Patients with cerebrovascular events 2/31 (6%)	0.0 (0.0, 3.2) (p = 0.14)

Note: Clinical event = renal or cardiac or cerebrovascular event
Renal event (33% increase in serum creatinine on two consecutive occasions or ESRD requiring long-term dialysis or transplantation); cardiac event (infarction, new symptomatic arrhythmia requiring antiarrhythmic medication, pacemaker or cardioversion or defibrillator implantation, unstable angina with EKG changes requiring hospitalisation, heart failure requiring hospitalisation); cerebrovascular event (stroke or transient ischemic attack document by physician).
[a] Post-hoc secondary analyses: protocol adherent patients – hazard ratio 0.39 (95% CI: 0.16, 0.93, p = 0.034); patients with GFR > 55 ml/min – hazard ratio 0.19 (95% CI: 0.05, 0.82, p = 0.025); patients with GFR < 55 ml/min – hazard ratio 0.85 (95% CI: 0.32, 2.3, p = 0.75)

The 18 month study by Banikazemi et al (2007) identified a statistically significant reduction in risk of clinical events (based on post-hoc analyses of protocol adherent patients) and a non-significant trend towards agalsidase beta delaying time to first event (renal, cardiac, cerebrovascular event or death) compared to placebo. Clinical events have not been reported as outcomes in agalsidase alfa trials.

An indirect comparison of Fabry patients treated with agalsidase alfa at 0.2 mg/kg biweekly or agalsidase beta at 1.0 mg/kg biweekly provided no clear conclusion in the comparative rate of change of eGFR in patients. A comparison of results from Schiffmann et al (2001) and Eng et al (2001) suggested more responders for both renal and cardiac GB3 clearance in patients treated with agalsidase beta compared to agalsidase alfa. However, the PBAC agreed that there was methodological confounding around these results, particularly related to the methods of detection of GB3.

With respect to the impact of either product on cardiac outcomes, Vedder et al (2007) showed no effect when both products were dosed at 0.2 mg/kg biweekly, however Beer et al (2006), Imbriaco et al (2009) and Weidemann et al (2003, 2009) reported that left ventricular mass and measures of myocardial function were improved with agalsidase beta (1.0mg/kg biweekly) treatment. Hughes et al (2008) and Baehner et al (2003) reported improved left ventricular mass in patients treated with agalsidase alfa. However,

it was noted 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.

The results for renal and cardiac GB3 clearance are presented in the table below.

Renal and cardiac GB3 clearance in agalsidase alfa and agalsidase beta trials

Trial ID	Outcome	Agalsidase	Placebo	p-value
Agalsidase alfa vs placebo				
Schiffmann et al (2001)	Kidney GB3 (nmol/mg tissue)	Mean baseline 19.5 (SE 1.68), mean final 15.6 (SE 1.60)	Mean baseline 19.0 (SE 3.59), mean final 18.1 (SE 3.18)	Change from baseline (p = 0.27)
Hughes et al (2008)	MRI change in LV mass (g)	-11.5	21.8	0.041
	ECG change in LV mass (g)	-6.2%	6.3%	> 0.05
	QRS duration (ms)	-12.9	4	0.8
Schiffmann (2001)	Mean change in QRS complex duration (ms)	-2.4	3.6	0.047
Agalsidase beta vs placebo				
Eng et al (2001)	Proportion kidney GB3 free[a]	20/29 free of kidney GB3 (69%)	0/29 free of kidney GB3 (0%)	Chi-square test (p < 0.001)
	Kidney GB3 score[a]	Mean baseline 1.9 (SD 0.8), mean final 0.4 (SD 0.7)	Mean baseline 2.2 (SD 0.7), mean final 2.1 (SD 0.8)	Change from baseline (p < 0.001)

Abbreviations: SD, standard deviation; SE, standard error

[a] Pathologist histology score for GB3 clearance, scale 0-3 with 0 score indicating only trace amounts of GB3 and 3 score indicating large accumulations of GB3 ECG, electrocardiogram; LV, left ventricular; MRI, magnetic resonance imaging.

Both treatments appeared to have similar safety profiles however agalsidase beta may have a less favourable immunogenicity profile. IgE antibodies as well as a higher frequency of IgG antibodies have been reported with agalsidase beta compared to agalsidase alfa. The implication of these antibody responses is unclear.

7. Clinical Claim

Agalsidase alfa

The submission from the sponsor of agalsidase alfa described agalsidase alfa as equivalent in terms of comparative efficacy to agalsidase beta. The submission claimed that the current evidence (direct and indirect) for both products could not distinguish any clear advantage of either product at the approved dose. The submission suggested that it is reasonable to assume that the agalsidase treatments are equi-effective in the absence of any direct comparison between treatments at their approved doses.

Agalsidase beta

The submission from the sponsor of agalsidase beta described agalsidase beta as superior in terms of comparative efficacy over agalsidase alfa. The submission claimed that the current body of evidence demonstrated that agalsidase beta treatment at the TGA approved dose of 1 mg/kg biweekly improves clinical outcomes, renal outcomes and cardiovascular outcomes in Fabry disease patients. The submission appeared to suggest that equivalence between agalsidase treatments could not be assumed without sufficient

evidence that agalsidase alfa can improve outcomes similarly to agalsidase beta (e.g. clinical, renal, cardiovascular) in Fabry disease patients.

The PBAC considered that there are significant areas of uncertainty regarding the evidence of comparative effectiveness of agalsidase alfa versus agalsidase beta. The PBAC noted that against most of the surrogate outcomes there appears to be no significant difference between the two agents, although there seems to be a trend which favours higher doses used in agalsidase beta. The clinical outcomes reported for agalsidase beta have not been reported for the alfa form but the PBAC regarded that this is not evidence of superiority for agalsidase beta. The PBAC also noted that switching between the products in Australia rarely occurs which suggests that they may have similar patient-relevant outcomes.

The PBAC concluded that the optimal doses for agalsidase alfa and agalsidase beta are uncertain and that there was an insufficient scientific basis at the time of the review for the dose difference between these agents based on clinical or physiochemical endpoints. The PBAC noted that while the beta form may stimulate the greater production of antibodies (of the small number of patients analysed for anti-agalsidase antibodies in Vedder et al (2007), anti-bodies were found in 4 out of 8 agalsidase alfa patients versus 6 out of 8 agalsidase beta patients) which may result in a greater dose requirement, the data to support this hypothesis are uncertain.

8. Recommendation and Reasons

The PBAC recommended that the price of agalsidase beta (Fabrazyme®) be reduced to meet the cost on a per patient basis of agalsidase alfa (Replagal®) on the basis that there is insufficient evidence at this stage to support a finding that there is any clinical difference between the alfa and beta forms at the registered doses.

The PBAC noted that the amino-acid sequences of both products are identical. In terms of glycosylation, the oligosaccharide side chains are similar in both products, however there are some slight differences, namely that agalsidase beta (which is produced from cultured CHO cell lines) has a higher proportion of mannose-6-p (which is required for binding to target cells and delivery to the lysosome) compared to agalsidase alfa which is carries the same glycosylation profile as the native human enzyme. The pharmacokinetic characteristics of the products are also similar, with receptor binding improved in agalsidase beta compared to agalsidase alfa, but no difference in fibroblast uptake at 10 hours after dosing. The study Blom et al (2003) showed that functional correction of Fabry fibroblasts in vitro for both products is also identical at identical molar exposure (0.1 mmol per hour for 3 hours).

The PBAC agreed that overall there is neither biochemical nor pharmacokinetic evidence to explain the five-fold dose difference (alfa 0.2 mg/kg every other week versus beta 1.0 mg/kg every other week) between agalsidase alfa and agalsidase beta.

There are no published randomised controlled trials comparing agalsidase alfa and agalsidase beta at their approved doses. The only published head-to-head trial of agalsidase treatments compared both treatments at the same dose of 0.2 mg/kg every other week (Vedder et al 2007). The dose of agalsidase beta used in this study was lower

than currently recommended (1.0 mg/kg every other week) with high rates of treatment failure noted by the authors in both treatment groups at a dose of 0.2 mg/kg biweekly.

Vedder et al (2007), the head-to-head study which forms part of the scientific basis of comparison in the literature review, showed no significant differences between treatments when agalsidase alfa and agalsidase beta were compared at identical doses of 0.2 mg.

The PBAC considered that overall many of the dose-ranging studies included in the submissions were inadequate to determine the optimal dose, since they are all short term studies (i.e. 10 weeks). All studies used plasma GB3 levels as their primary endpoint, with no differences shown between 0.2 mg/kg biweekly and higher doses for agalsidase alfa (including 0.4 mg/kg biweekly, 0.2 mg/kg weekly and 0.4 mg/kg weekly). One study, Eng et al (2001b), suggested faster GB3 clearance at higher doses for agalsidase beta, however the clinical relevance of these outcomes remains unclear, given the chronicity of the condition. Two longer term (24 months) studies, of poor design, investigating non-approved dosage regimens compared agalsidase alfa 0.2 mg/kg at dosing frequencies of weekly and biweekly (Shiffmann et al (2007) and found no changes in plasma or urine GB3, but a reduced rate of decline in eGFR, with increased dose frequency). Lubanda et al (2009) found no significant difference in tissue, plasma or urine GB3 when agalsidase beta patients had their doses reduced from 1.0 mg/kg biweekly to 0.3 mg/kg biweekly.

In terms of clinical outcomes, an indirect comparison of Fabry patients treated with agalsidase alfa at 0.2 mg/kg biweekly or agalsidase beta at 1.0 mg/kg biweekly provided no clear conclusion in the comparative rate of change of eGFR in patients. A comparison of results from Schiffmann et al (2001) and Eng et al (2001) suggest more responders for both renal and cardiac GB3 clearance in patients treated with agalsidase beta compared to agalsidase alfa, however, it was noted there was methodological confounding around these results, particularly related to the methods of detection of GB3.

Vedder et al (2007) showed no effect of either product on cardiac outcomes when both products were dosed at 0.2 mg/kg biweekly, however Beer et al (2006), Imbriaco et al (2009) and Weidemann et al (2003, 2009) reported that left ventricular mass and measures of myocardial function were improved with agalsidase beta (1.0 mg/kg biweekly) treatment. Hughes et al (2008) reported improved left ventricular mass in patients treated with agalsidase alfa. However, the clinical relevance of left ventricular mass as an outcome in Fabry patients, who tend to suffer poor diastolic function, was questioned.

The PBAC considered that there are significant areas of uncertainty regarding the evidence of comparative effectiveness of agalsidase alfa versus agalsidase beta. The PBAC noted that against most of the surrogate outcomes there appears to be no significant difference between the two agents, although there seems to be a trend which favours higher doses used in agalsidase beta. The clinical outcomes reported for agalsidase beta have not been reported for the alfa form but the PBAC regarded that this is not evidence of superiority for agalsidase beta. The PBAC also noted that switching between the products in Australia rarely occurs which suggests that they may have similar patient-relevant outcomes.

The PBAC concluded that the optimal doses for agalsidase alfa and agalsidase beta are uncertain and that there was an insufficient scientific basis at the time of the review for the dose difference between these agents based on clinical or physicochemical endpoints. The PBAC noted that while the beta form may stimulate the greater production of antibodies which may result in a greater dose requirement, the data to support this hypothesis are uncertain.

The PBAC indicated its willingness to reconsider the situation when more definitive data become available. The PBAC noted that the Canadian Fabry Disease Initiative Study of enzyme replacement therapy for Fabry disease is in progress which is the first head-to-head comparison of the agalsidase treatments at their approved doses.

9. 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.

10. Sponsors' Comment

Genzyme reaffirms its views on the clinical evidence, comparative effectiveness and dosing of agalsidase beta as outlined under '7. Clinical Claim *Agalsidase beta*'.

Shire maintains its position regarding agalsidase alfa as described under '7. Clinical Claim *Agalsidase alfa*'.