All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Agalsidase alfa (Replagal®)
Shire Human Genetic Therapies

Advice No: 1107 – October 2007

Recommendation of AWMSG

Agalsidase alfa (Replagal®) should be recommended for use within NHS Wales as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease.

Patients receiving agalsidase alfa (Replagal®) will be entered into the Fabry Outcomes Survey. AWMSG urge the manufacturers of agalsidase alfa and agalsidase beta to develop a combined outcomes database.

Treatment will be administered under the supervision of a physician experienced in the management of Fabry disease or other inherited metabolic diseases.

Treatment will be administered according to agreed guidelines at appropriate designated centres.

AWMSG will review this and other enzyme replacement therapies within three years.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

Date: 18th October 2007

The recommendation of AWMSG is:

Agalsidase alfa (Replagal®) should be recommended for use within NHS Wales as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease.

Patients receiving agalsidase alfa (Replagal®) will be entered into the Fabry Outcomes Survey. AWMSG urge the manufacturers of agalsidase alfa and agalsidase beta to develop a combined outcomes database.

Treatment will be administered under the supervision of a physician experienced in the management of Fabry disease or other inherited metabolic diseases.

Treatment will be administered according to agreed guidelines at appropriate designated centres.

AWMSG will review this and other enzyme replacement therapies within three years.

2.0 PRODUCT DETAILS:

2.1 Licensed indication[1]:
Agalsidase alfa (Replagal®) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).

2.2 Dosing[1]:
Agalsidase alfa is administered at a dose of 0.2mg/kg body weight every other week by intravenous infusion over 40 minutes. Subsequent to trial work, this dosage regimen is suggested for children between seven and 18 years of age[1]. No dosage regimen is presently recommended in children up to and including six years old[1].

2.3 Market authorisation date: 3rd August 2001[1]

2.4 UK Launch date: 2001[2]

3.0 DECISION CONTEXT
Anderson-Fabry disease (known as Fabry disease) is an X-linked recessive lysosomal storage disorder, due to a deficiency of α-galactosidase A (α-Gal A)[3]. As a result of this enzyme deficiency, glycosphingolipids, in particular globotriaosylceramide (Gb_3), accumulate in the lysosomes of the vascular endothelium causing progressive organ damage involving the skin, liver, kidneys, heart and nervous system[3]. Males are predominantly affected and the onset and progression of serious manifestations can vary widely[4]. Females are carriers and though some females may develop the same symptoms of the disease, incidence is in general lower, onset is later and usually the severity reduced [5,6].

Many carriers can essentially be disease free, however in classically affected males, presentation is usually in childhood or adolescence. The first symptom is often acroparaesthesia, a recurrent, severe debilitating neuropathic (burning) pain in the hands and feet, which can greatly impair quality of life [7,8]. Other clinical features include skin lesions, corneal opacities (vision not affected), progressive hearing loss, diarrhoea, chronic weight loss and hypohidrosis. After the age of 30, most affected males will suffer from renal failure. End stage renal failure is usually reached between 40 and 50 years of age in male patients[9]. The median survival time for males is about 50 years and 70 years for females representing an approximate life span reduction of 20 and 15 years, respectively when compared with the general population[4]. Patients usually die prematurely from complications of end stage renal disease, cardiac disease or stroke [3].

Treatment in the past has tended to be supportive, with symptomatic management such as analgesia, antihypertensives, anti-arrhythmics and anticoagulants. Renal transplantation and dialysis may be required in the latter stages of the disease[3]. Progress in the application of molecular genetic techniques has lead to the development of enzyme replacement therapy (ERT), which aims to supply the deficient enzyme to the lysosomal cells where storage product accumulates. Currently, agalsidase alfa (Replagal®) is one of two enzyme preparations licensed for long term ERT in patients with a confirmed diagnosis of Fabry disease (α-galactosidase deficiency)[1,10]. The All Wales Medicines Strategy Group appraised the alternative product, agalsidase beta (Fabrazyme®) in October 2006 (refer to section 9.3) [11,12].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

In the clinical trials reviewed, agalsidase alfa when compared to placebo showed improvement in all the parameters assessed, and demonstrated that there is some benefit to treatment. Data is currently limited, in particular for children, patients with more advanced disease and patients with variant forms of the disease. It should be noted ERT, for any patient, is life long. AWMSG are of the opinion that further longer term data that focuses on clinical outcomes, including survival, are required in order to provide clearer evidence of the efficacy of agalsidase alfa in treating and preventing manifestations of Fabry disease in patients.

4.2 Review of the evidence on cost effectiveness

The economic model presented for agalsidase alfa compares the drug against usual symptomatic care. Agalsidase beta was not considered as a comparator, but may be relevant if patients that are treated with agalsidase beta switch to agalsidase alfa (as is specified implicitly in the budget impact analysis). Several assumptions are made relating to the efficacy of agalsidase alfa, which are overoptimistic and significantly bias the model in its favour; however, the incremental cost per QALY still exceeds £250,000. When tested in plausible but limited sensitivity analysis, the estimated incremental cost per QALY gained was significantly higher than in the base-case analysis, indicating that the outputs of the model are sensitive to the assumptions made around the efficacy of the drug. In addition, there appears to be errors in the calculation of the results of this sensitivity analysis, which adds to the uncertainty of the estimated cost-effectiveness.

AWMSG is mindful of the ultra-orphan drug status of agalsidase alfa. However, there is no evidence presented to suggest that agalsidase alfa serves to bridge a gap to a "definitive" therapy, or that this "definitive" therapy is currently in development. The case for agalsidase alfa representing an innovative advance on existing therapy has not been demonstrated, and AWMSG is aware of the opinion that agalsidase alfa may not represent efficient use of healthcare resources.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Studies are extremely limited in children and have not been performed in patients over the age of 65 years. Therefore safety and efficacy in these patient populations have not yet been established[1].
- Limited data are available in patients on dialysis or post kidney transplantation[1].
- No studies have been performed in patients with hepatic impairment[1].
- A head to head trial comparing agalsidase alfa to the alternative ERT agalsidase beta would be required to provide clear evidence of their relative efficacy in preventing and treating meaningful manifestations of Fabry disease.
- There is currently a lack of detailed information regarding the advantages and disadvantages of receiving agalsidase alfa in the home setting.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company submission[13] includes a pivotal Phase II randomised, double blind, placebo controlled study (TKT003) and its open-label extension study (TKT006). These studies were designed to evaluate the efficacy and safety of agalsidase alfa in male patients with confirmed Fabry disease[14-16]. The pivotal trial and also two papers reporting on results from the extension study are outlined and discussed together

under section 6.1.4. The submission also includes an open label safety and efficacy trial of agalsidase alfa in female patients[17], as well as two clinical studies in children [18,19]. Safety data relating to all of these studies are discussed under section 6.2.

6.1.1 Study TKT003. Schiffmann R, Kopp J, Austin H et al. Enzyme replacement therapy in Fabry Disease. A randomised controlled trial. JAMA 2001; 285(21): 2743-49[14].

This was a Phase II/III, double blind, placebo controlled trial conducted from December 1998 to August 1999 at the Clinical Research Centre of the National Institutes of Health. The 24-week study evaluated the safety and efficacy of repeated intravenous agalsidase alfa given to patients with a confirmed diagnosis of Fabry disease. All 26 patients were hemizygous adult males with neuropathic pain (mean age, 34 years; range, 19.0 to 47.0 years). Fourteen patients were treated with agalsidase alfa (0.2mg/kg every two weeks) and 12 patients received placebo. Age, weight, race, duration and severity of illness, and levels of residual α-galactosidase A activity were comparable between the two groups.

The primary endpoint, the effect of therapy on neuropathic pain while without neuropathic pain medications, was assessed using question three of the Brief Pain Inventory (BPI) short form. Such medications were defined to include carbamazepine, gabapentin, phenytoin, lamotrigine, nortriptyline, and amitriptyline. At baseline and at weeks eight, 16 and 23, patients discontinued taking any neuropathic pain medications and completed the BPI within the following week, with precise timing based on the individuals analgesic requirements. A pain score of one to three represents mild; four to seven, moderate; and eight to ten, severe (refer to appendix 1 for further details). Other pain end points including pain-related quality of life were also assessed. Secondary endpoints based on clinical and biochemical measures included renal function, cardiac conduction, Gb_3, and antibody analyses.

Results:
The agalsidase alfa treatment group showed a consistent and progressive decline in pain scores 3.8 units (Standard Deviation [SD] 0.44 units) to 2.7 units (SD: 0.54 units) compared with no significant change in the placebo group[11]. Overall pain severity (p=0.02) and also pain-related quality of life (QoL) (p=0.05) improved significantly more with agalsidase alfa than compared with placebo. Four patients were able to discontinue their pain medications completely compared with none in the placebo group (p=0.3, non significant).

There was a documented improvement in secondary end points. Renal outcomes indicated a significant improvement in creatinine clearance (p=0.02), and changes in renal pathology[20]. Pathologists performed (at baseline and at week 24) renal biopsies. After six months there was a 21% increase in the fraction of normal glomeruliin the kidney, versus a 27% decrease in the placebo group (p=0.01). One patient in the placebo group progressed to end stage renal disease during the course of the study and began peritoneal dialysis. There was a significant improvement in cardiac conduction (p=0.047) and a decrease in urinary sediment Gb_3 in the agalsidase alfa patients compared with placebo (p=0.05). Plasma Gb_3 concentrations were reduced by 54% compared with 7% with placebo (p=0.005).

All but one patient (who withdrew at week 22 for personal reasons) completed the six month placebo controlled trial mentioned in section 6.1.1 and subsequently enrolled in an open label extension study. These patients (including those who had previously received placebo) were all treated every other week with agalsidase alfa (0.2mg/kg) infused intravenously. Published data available relating to this extension study

provides information on patients treated with agalsidase alfa for between 36 to 54 months.

6.1.2 Study TKT006. Schiffmann R, Floeter M, Dambrosia J et al. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry Disease. Muscle & Nerve 2003; 28: 703-10 [15].
This paper specifically examined the long term effects of agalsidase alfa on neuropathic pain, detection thresholds for warmth and cold, and sudation and included eleven patients who crossed over from placebo to ERT at the end of the controlled study (TKT003)[15]. Details of the methods used are outlined in the paper published by Schiffmann and colleagues[14].

Results:
At the 12-month time point (six months after the end of the controlled trial, patients who had previously received placebo demonstrated a significant improvement in neuropathic pain. Scores were similar to those observed in the original ERT group (p=0.015) with a mean decline of 2.6 units (SD: 0.9 units). Further reduction in pain scores did not occur after the first six months of ERT. Overall reduction in pain scores in both groups after 12 to 18 months of active therapy was 1.9 units ([SD: 0.53 units], p=0.003). that the total number of days that patients involved were able to remain off pain medications in the agalsidase alfa group was 93.5 days compared to 25.4 days in the placebo group (p=0.013) [20].

With regards to thermoperception, there was no significant difference after the six month controlled trial between the ERT and placebo groups for any of the sensory modalities. However, over three years of open label treatment, there was a significant reduction in the cold (p<0.001) and warmth (p=0.006) detection thresholds in the foot, and for warmth perception in the thigh (p=0.03).

Agalsidase alfa infusion caused an acute improvement in sweat function (0.57 ± 0.71 microlitres/mm^2 versus 0.24 ± 0.33 microlitres/mm^2, 24–72 hours after infusion versus baseline, mean ± SD, n = 17, p = 0.04) [15]. The therapeutic effect lasted for about seven days with a subsequent return to pre-infusion levels. Seven out of 17 patients remained non-responders. No benefit was reported for nerve conduction or clinically significant effects on vibration threshold.

6.1.3 Study TKT006. Schiffmann R, Ries M, Timmons M et al. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in the home setting. Nephrology Dialysis Transplantation 2006; 21: 345-54[16].
This paper reports long term safety data, and effects of agalsidase alfa on renal function and Gb_3 clearance for up to 48 months (n=20/25) or 54 months in the patients who had completed the original controlled study in the ERT group (n=9/14)(see section 6.1.1).

One patient received a kidney transplant prior to starting ERT, therefore, effects on renal function were evaluated in 24 patients. There was no specific requirement for renal dysfunction to be present at baseline. However, of these 24 patients, 12 had Stage I at baseline, eight had Stage II, and four had Stage III chronic renal disease (refer to appendix 1;table 1). Glomerular Filtration Rate (GFR) was used as a surrogate measure of renal function.

Results:
Overall, mean estimated GFR for the entire patient population remained relatively stable for up to 36–54 months of agalsidase alfa treatment (refer to appendix 1;

Table 2). A marked decline in GFR was noted in the four patients with stage III renal disease from baseline. In these patients, mean estimated GFR fell from 47.1±9.4 ml/min/1.73m^2 to 24.8±14.5ml/min/1.73m^2 (not statistically significant) after 48 months of therapy (representing an average rate of decline of 5.2 ml/min/1.73m^2 per year). None of these patients with Stage III renal disease progressed to end stage renal failure while receiving long-term ERT with agalsidase alfa.

Plasma Gb_3 decreased to a mean of 5.8±0.4 nmol/ml over the first six months of treatment with agalsidase alfa and remained decreased for the duration of the study ($p<0.001$ for all time points compared with baseline).

6.1.4 Points to note from study TKT003 and the extension TKT006[14-16]:

- There was no active comparator in this study.
- The use of surrogate markers makes it difficult to assess actual improvement in day-today function or morbidity.
- The pivotal trial, and therefore the open label extension study, included only adult males, and due to the rarity of the disease the trial population was small.
- Only patients in the active treatment arm of the double blind phase of the trial had the opportunity to be treated for 54 months. Twenty out of the 26 patients participating in the study completed 48 months and nine patients completed 54 months. One patient withdrew after 36 months of treatment with agalsidase alfa to enrol in a clinical trial with agalsidase beta. Withdrawals were not related to adverse effects.
- Trial evaluation of neuropathic pain (a clinically significant aspect of Fabry disease) was only measured for up to 12 to 18 months depending on whether patients had received ERT from the start of the study. Results show that pain was reduced, not abolished [20]. This study allowed participants other forms of pain medication while on treatment.
- The EPAR states that the exact magnitude of pain reduction and the effect on reversibility in renal pathology were more difficult to estimate due to methodological limitations[20].
- Further longer-term data are required in order to adequately assess the effect of agalsidase alfa on QoL, and also to evaluate survival.
- It was reported that the development of IgG antibodies did not appear to affect any clinical endpoints[16].
- It would appear that agalsidase alfa has an initial effect in stabilising then improving renal function with long-term treatment.
- After the first year of the open label study, a nurse could administer treatment at home. Twenty-two patients had infusions in the home setting. Schiffmann and colleagues report that the safety and feasibility of home infusion of agalsidase alfa was demonstrated during this long term, open label study[16], however this data is limited. A satisfaction survey of 20 patients receiving agalsidase alfa at home has been referenced in the company submission[13, 21].

6.1.5 Study TKT014. Baehner F, Kampmann C, Whybra C et al. Enzyme replacement therapy in heterozygous females with Fabry disease: Results of a phase IIIB study. Journal of Inherited Metabolic Disease 2003; 26: 617-27[17].

This open label study evaluated the safety, efficacy and pharmacokinetics of agalsidase alfa administered intravenously to 15 adult female patients with confirmed Fabry disease (mean age, 45.3 years; range, 20 to 66 years). Patients were eligible for enrolment if they had clinical evidence of Fabry disease involving at least three organs. Evidence could include neuropathic pain, a history of cerebrovascular accident, left ventricular hypertrophy, or renal function consistent with Fabry disease.

All patients received a dose of 0.2mg/kg agalsidase alfa intravenously every two weeks for up to 55 weeks. Since patients were enrolled consecutively and the study was concluded after European Union regulatory approval was granted, the number of doses and thereby the duration of observation varied (between 13 to 41 weeks) depending on when the patient was enrolled.

This study aimed to report clinical measures including safety evaluations, renal function, cardiac disease, and QoL as assessed using the Short Form 36 (SF-36) questionnaire (refer to appendix 1).

Results:
Renal function was assessed by serial measurement of creatinine clearance over 24hrs. Creatinine clearance remained stable throughout the study, with mean values ranging from 65 to 73ml/min/1.73m^2. There was progressive decline in the left ventricular (LV) mass index (grams per m^2) over the duration of the study, with statistically significant change from baseline in LV mass at Week 27 (n=11: -23.0 [SD: 5.78], p=0.003) and Week 41 (n=7: -25.2 [SD: 8.12], p=0.021). The mean QRS duration which is a surrogate measure of cardiac function decreased progressively from baseline to Week 41. A statistically significant mean decrease was observed from baseline at Week 27 (n=11: -8.7 [SD: 2.6], p=0.007), but not at Week 41 (n=5: -3.6 [SD:1.83], p=0.121). Mean QoL scores increased across the study period and, when measured at Week 27, improvements in QoL were statistically significant for the summary component of physical functioning (n=10, $p < 0.025$) as well as the individual scales of physical functioning; role-physical (n=11, $p < 0.00625$) and general health (n=11, $p < 0.00625$). Gb_3 levels in plasma and urinary sediment decreased significantly at Week 13 ($p \leq 0.03$)[13]. Eleven patients completed Week 27, but for this subgroup the changes were not significant[17].

Points to note from the study:

- Due to the rarity of the disease the data is limited to a small number of female patients. In addition, only the first eight patients enrolled in the trial received at least 20 infusions of agalsidase alfa (over 41 weeks); the next three patients received between 14 and 18 infusions (over 29 to 37 weeks), and the last four patients received eight to nine infusions (over 17 to 19 weeks).
- Further longer term data that focuses on clinical outcomes, including survival, is required in order to provide clearer evidence of the efficacy of agalsidase alfa in treating and preventing manifestations of Fabry disease in female patients.
- The pharmacokinetic profile of agalsidase alfa from this study of female patients was reported to be comparable to the pharmacokinetics of agalsidase alfa in male patients.

6.1.6 Study TKT023. Ries M, Clarke J, Whybra C et al. Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. Pediatrics 2006; 118:924-32 [18].

This six-month open label study aimed to evaluate the safety and explore the efficacy of agalsidase alfa therapy in 24 paediatric patients with Fabry disease between the ages of 6.5 and 18 years (19 boys and five girls; mean age, 11.8 years). All patients were naïve to ERT and given agalsidase alfa 0.2mg/kg intravenously every two weeks for the duration of the study. Assessments included the effect of agalsidase alfa infusion on neuropathic pain, renal function, cardiac structure, sudation and Gb_3 clearance, although manifestations in these parameters were typically mild to begin with. The majority of patients in this study had normal or near normal quality of life that remained stable over the 26 weeks of the study. The boys showed a significant

reduction in plasma Gb_3 on treatment ($p < 0.001$), but no significant changes in the other measurements were reported. However, six out of 11 patients on anticonvulsants for neuropathic pain were able to reduce or discontinue their use ($p=0.012$). Although non-significant, an increase in mean sweat volume ($p=0.06$) was also reported.

6.1.7 Study TKT5S-001. Ramaswami U, Wendt S, Pintos-Morell G et al. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease. Acta Paediatrica 2007; 96: 122-27[19].

Thirteen children with Fabry disease (nine boys and four girls) took part in this open-label study with a median age at the start of the study of 11.0 years (range, 3.5 to18.0 years). All patients received agalsidase alfa (0.2 mg/kg every two weeks) over a 23- week period. The authors of this publication concluded that agalsidase alfa appeared to have beneficial effects on the neurological symptoms of Fabry disease, decreasing the levels of pain in most patients with pain at baseline, and preventing the further development of pain symptoms in patients with minimal pain at baseline. Short term improvements in sudation were noted in three out of five boys and in one of the girls tested after 23 weeks of treatment.

All male patients had increased plasma levels of Gb_3 at baseline (range, 4.3–10.8 μmol/l), whereas levels in females were within the normal range (range, 2.3–3.3 μmol/l). Plasma concentrations of Gb_3 decreased in the male patients towards the normal range after 12 and 23 weeks of treatment and declined slightly in the female patients[13].

Points to note:

- The statistical significance of these observations has yet to be established.
- Boys had confirmed laboratory evidence of α-galactosidase A deficiency. In girls, Fabry disease was confirmed by genetic analysis.
- Evidence in these studies is limited to short-term data. Further longer-term data that focuses on clinical outcomes, including survival, is required in order to provide clearer evidence of the efficacy of agalsidase alfa in treating and preventing manifestations of Fabry disease in children.
- Further studies are also needed in order to establish when treatment should be initiated, and to provide more data on the effect of treatment on the quality of life in children.

6.1.8 The Fabry Outcome Survey (FOS)

The company have also highlighted in their submission the FOS. This is supported by the company and is distinct from the Fabry Registry (see section 9.4). The FOS is a multinational multicentre database of all patients with Fabry disease who are receiving, or are candidates for ERT with agalsidase alfa. It was developed in 2001 to gain further understanding of the nature of Fabry disease and to assess the long-term safety and efficacy of agalsidase alfa in Fabry disease.

The inclusion criteria of FOS are broader than in clinical trials and there are a wider spectra of coexisting illnesses, disease severity and concomitant treatments, such that FOS data may provide a better representation of the population of patients with Fabry disease as a whole. Key findings from this survey were outlined in Form B, along with a full list of FOS publications to date shown in Appendix B of the company's submission.

6.1.9 Additional studies

Two additional studies were also highlighted in the company's submission regarding cerebral blood flow abnormalities in patients with Fabry disease[13]. The long-term clinical implications from the observations made in these studies have yet to be established.

6.2 Safety:

In general treatment with agalsidase alfa would appear to be reasonably well tolerated and clinical trials reported most undesirable effects as mild to moderate in severity[1]. During the 48 to 54 months of the pivotal trial and extension study (TKT003 and TKT006) the majority of adverse effects observed in the male participants were reported as consistent with the natural history of untreated Fabry disease and were not attributed to agalsidase alfa therapy with the exception of infusion related reactions[14]. There were 13.7% of patients treated with agalsidase alfa reported in clinical trials as having experienced idiosyncratic infusion related reactions. Overall, the percentage of such reactions was significantly lower in females than males[1]. The most common symptoms have been rigors, headache, nausea, pyrexia, flushing and fatigue. The onset of infusion related reactions has generally occurred within the first two to four months after initiation of treatment and these effects have decreased with time. Patients usually respond to reducing the infusion rate or administering oral or intravenous pre-treatment with antihistamines and/or corticosteroids. As with any intravenous protein product, allergic type hypersensitivity reactions are possible. If this occurs agalsidase alfa should be discontinued immediately and appropriate emergency treatment initiated[1].

Furthermore patients may develop IgG antibodies to the protein. A low titre IgG antibody response has been observed in approximately 24% of the adult male patients treated with agalsidase alfa. Based on limited data this percentage has been found to be lower (7%) in the paediatric male population. These IgG antibodies appeared to develop following approximately three to 12 months of treatment. After 12 to 54 months of therapy, 17% of treated patients were still antibody positive whereas 7% showed evidence for the development of immunologic tolerance, based on the disappearance of IgG antibodies over time. The remaining 76% remained antibody negative throughout. The clinical trial in 15 adult females found that no patient developed antibodies to agalsidase alfa[17]. No IgE antibodies have been detected[1].

The presence of extensive renal damage may limit the renal response to ERT, possibly due to underlying irreversible pathological changes. In such cases, the loss of renal function remains within the expected range of the natural progression of disease[1].

Adverse drug reactions reported in patients with history of end stage renal disease were similar to those reported in the general population. In addition, those reported in paediatric patients were, in general, similar to those reported in adults [1,18,19]. However, infusion related reactions and pain exacerbation occurred more frequently in the children and adolescents studied[1].

Agalsidase alfa should not be co-administered with chloroquine, amiodarone, or gentamicin since these substances have the potential to inhibit intra cellular α-galactosidase activity. As α-galactosidase A is itself an enzyme, it would be an unlikely candidate for cytochrome P450 mediated drug-drug interactions. In clinical studies, medicinal products used to treat neuropathic pain (such as carbamazepine,

phenytoin and gabapentin) were administered concurrently to most patients without any evidence of an interaction [1,14].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

Fabrazyme® (agalsidase beta) is currently the only alternative ERT licensed for the treatment of Fabry disease. It is a recombinant human α-galactosidase produced by genetically engineered Chinese Hamster Ovary (CHO) cells[10]. The majority of patients develop IgG antibodies to this treatment, but demonstrate a significant reduction in antibody titre over time (approximately 35% plateau)[10]. IgE antibodies have been identified in some patients treated with agalsidase beta [10]. Fabryzyme® as well as Replagal® has a suggested dosage regimen for use in children. In the case of Fabrazyme® the adults dosage regimen is recommended for use in children aged eight to 16 years old.

7.2 Comparative effectiveness:

- There are no comparative trial data for agalsidase alfa and beta formulations. Many of the trials have used different entry criteria, which makes indirect comparisons difficult.
- Studies have predominantly focused on surrogate markers rather than clinical outcomes.
- Further work is required to establish the clinical efficacy for algalsidase alfa, in particular for children, patients with more advanced disease and patients with variant forms of the disease.
- Studies to confirm dosing schedules are currently being undertaken [23,24]. Studies are also warranted to confirm when treatment with agalsidase alfa should be initiated.
- There is no comparable alternative to ERT at this time.
- In contrast to agalsidase beta, agalsidase alfa is a highly purified form of the naturally occurring human lysosomal hydrolase enzyme. The dosage for each drug is not the same and may be due to differences in receptor uptake. The infusion time for agalsidase alfa of 40 minutes, as opposed to a minimum of two hours for agalsidase beta may be an advantage.
- Limited information is available regarding the advantages and disadvantages of administering agalsidase alfa in the home setting.
- No information is currently available regarding the effectiveness of switching from one ERT preparation to another.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether the additional benefits offered by agalsidase alfa over the relevant comparator (usual care with symptomatic treatment of co-morbidities, or treatment with agalsidase beta) justify the additional costs.

8.2 Review of published evidence on cost-effectiveness

A Health Technology Assessment of enzyme replacement therapy (ERT) for Fabry disease was published in 2006[6]. This included an economic model (Connock model) that formed the basis of the company submission. The authors of the company model identified a number of limitations and a range of assumptions in the Connock model that significantly favoured ERT versus the comparator of usual symptomatic care. These included the assumption that ERT was 100% effective in all treated patients and returned their life expectancy and quality of life to that of the population norm. The Connock model was run using agalsidase beta as the

ERT[6], but in all respects other than cost, the model assumptions would have been equally applicable to either agalsidase beta or agalsidase alfa.

8.3 Review of company submission on cost-effectiveness

8.3.1 Summary of the evidence

The agalsidase alfa model is developed from the Connock model methodology but attempts to improve on some of the assumptions made. The adjustments that have been made, however, primarily relate to the modelling of the disease state rather than the effectiveness of treatment. The most significant limitations and assumptions used in the Connock model, which are essential to the estimation of quality adjusted life years (QALYs) gained, still remain in the agalsidase alfa model.

Agalsidase alfa plus usual care is compared with usual care. A hypothetical cohort of 1000 male and female patients with a mean body weight of 50kg is simulated from the point of diagnosis until death. None of the main clinical inputs are derived directly from the clinical trial data for agalsidase alfa. Instead, utility values and mortality data have been largely obtained or derived from other sources and assumptions made in their application. In the base-case, the model assumes that all patients who receive treatment with agalsidase alfa immediately become asymptomatic and have a normal life expectancy. These assumptions are unlikely and significantly bias the model in favour of agalsidase alfa. Adverse events are not considered in the model.

The model considers only the direct annual costs of Fabry disease complications (i.e. costs of usual care), which are taken from or calculated from a range of published sources (including the Connock model), and the direct costs of agalsidase alfa treatment. In the base-case analysis, it is assumed that there is no wastage of agalsidase alfa, i.e. complete vials are used, despite this not being in accordance with the SPC[1].

Three one-way sensitivity analyses are presented, which explore the assumptions of mean body weight, drug wastage and 100% efficacy. However, there appear to be a number of errors in the calculation and presentation of the results.

8.3.2 Summary of the key findings

In the base-case analysis, patients have a mean weight of 50kg (assumed average weight across adults and children), regain full health when agalsidase alfa is started, treatment is 100% effective and there is no drug wastage from the use of vials. The ICER for agalsidase alfa versus usual care was estimated as £252,951 per QALY gained. This is based on additional lifetime costs of £887,858 and a gain of 3.51 QALYs versus usual care[11].

For comparison, the same scenario in the Connock model resulted in an ICER for agalsidase beta versus usual care of £252,112 per QALY gained. This was based on additional costs of £2,537,792and a gain of 10.07 QALYs versus usual care[6].

In the sensitivity analyses, adjustment of mean body weight to 70.39kg increased the ICER to £359,597 per QALY gained. Separately reducing efficacy to 75% was reported to increase the ICER to £323,839 per QALY gained. However, there appear to be a number of errors in the calculation and presentation of this result, which prevents its interpretation.

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence

The company submission assumes there are 30 patients with Fabry disease in Wales. This is taken from the WMP assessment of agalsidase beta[11]. The prevalence is assumed to be 1:100,000 [11]. The budget impact analysis estimated the distribution of costs associated with

agalsidase alfa over the next five years using a bootstrapping approach. A total of 1000 cohorts of 30 patients with different baseline characteristics of weight, sex and symptoms/co-morbidities were simulated by random sampling. The model assumed patients to be symptomatic. In the absence of any supporting data, the probability of exclusion from treatment due to factors such as pregnancy, side effects, etc. was assumed to be 5%. The base-case analysis uses the same assumptions around effectiveness, mean body weight and no drug wastage, as used in the cost effectiveness model. Three other scenarios were reported as sensitivity analyses.

8.4.2 Summary of the key findings

In the base-case analysis, the budget impact model estimates the cost of agalsidase alfa to be £2.43million in year one, increasing to £2.46million in year five due to a 1.1% net increase in the population size. This is based on a mean patient weight of 50kg, 100% effectiveness and no drug wastage.

In sensitivity analyses, adjustment of the mean body weight of patients to 70.39kg increased the agalsidase alfa treatment costs to £3.41million in year 1, and to £3.45million in year 5. This scenario was also used to compare the budget impact of agalsidase alfa with that estimated for agalsidase beta in the WMP assessment of agalsidase beta[11]. In year one, the budget impact of agalsidase beta was estimated as £3.54million[11]. The authors of the agalsidase alfa submission suggest that treatment of all patients in Wales with agalsidase alfa instead of agalsidase beta could save £129,000 per year. However, the model designs are not directly comparable.

The combined effect of reduced efficacy (75%), randomly sampling body weight from a normal distribution with a mean of 70.39kg, under the assumption of drug wastage, agalsidase alfa treatment costs increases to £3.84million in year one, and to £3.88million in year five, i.e. 58% higher than in the costs estimated in the base-case analysis.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- In October 2004 the Department of Health (DoH) issued a statement on the 'national designation and funding of the service for patients with lysosomal storage disorders' in England [25]. Physicians working with the National Specialist Commissioning Advisory Group (NSCAG) in England have recently updated clinical guidelines for the diagnosis and management of Fabry disease [26]. The adoption of these guidelines within Wales may be considered.
- A physician experienced in the management of patients with Fabry disease, or other inherited metabolic diseases must supervise treatment with agalsidase beta. Patients are likely to be initially assessed in a tertiary hospital site.
- Given the geography of Wales and the fact the drug is administered every two weeks, a system for administration could be established using hospitals more local to patients' homes. This system is already employed by the NSCAG centres in England.
- The Summary of Product Characteristics for Replagal® states that home therapy may be considered[1].
- It is the view of AWMSG that, in the context of primary care, agalsidase alfa is not currently suitable for shared care.

9.2 Related advice:

Due to the complexity of the disease it has been debated when treatment should be initiated. A consensus group of Fabry disease experts met in 2003, the conclusions

drawn from this suggested that ERT should be used in young patients to prevent disease, and in older patients to halt disease progression[3].

In 2006 the NHS Health Technology Assessment programme carried out a systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry disease and mucopolysaccharidosis type I [6]. Connock and colleagues summarised that, in general the studies reviewed varied widely in design, quality and end points measured, making robust conclusions about effectiveness difficult. In order to overcome limited evidence on the natural history of the disease and the clinical effectiveness of the intervention (i.e. ERT), the report suggests the establishment of a disease-specific data registry to facilitate the process of technological assessment and improving patient care[6].

9.3 Previous AWMSG/NICE advice

In October 2006, the All Wales Medicines Strategy Group recommended the use of agalsidase beta (Fabrazyme®) within NHS Wales for Fabry disease with the following restrictions[10,11]:

- Patients receiving algalsidase beta (Fabrazyme®) will be entered into the Fabry registry.
- Treatment will be administered under the supervision of a physician experienced in the management of Fabry disease or other inherited metabolic diseases.
- Treatment will be administered according to agreed guidelines at appropriate centres.

This advice was subsequently endorsed by the Minister for Health and Social Services[12].

9.4 Registries

- The Fabry Registry collects information about the disease and patient outcomes in relation to ERT and other aspects of the disease [27].
- The Canadian Fabry Disease Initiative (CFDI) will determine the impact of ERT on the development of complications of Fabry disease in males and females currently on, or who have received ERT; and to assess which of these complications respond to the ERT therapy. Another purpose of this study is to establish a national registry, which will collect information on all persons with Fabry Disease in Canada[28].

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Appendix 1. Additional Clinical Information

- **TABLES**

Table 1. The National Kidney Foundation. Chronic Kidney Disease classification[29]

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Table 2. Estimated GFR (ml/min/1.73m2) in patients receiving agalsidase alfa for up to 54 months in Study TKT 006[13,16].

	Baseline (mean ± SD)	Final (mean ± SD) (48 or 54 months data)
Stage I CKD (n = 12)	108.7 ± 14.1	101.5 ± 12.4
Stage II CKD (n = 8)	78.6 ± 8.2	67.1 ± 17.0
Stage III CKD (n = 4)	47.1 ± 9.4	25.1 ± 16.4

- **THE BRIEF PAIN INVENTORY (BPI) SHORT FORM[30]**

This form contains nine pain-related questions, each answered by circling a number on a scale of 0 to 10. Patients, at baseline, completed the BPI, and again during each visit to the National Institutes of Health for the enzyme infusion, as well as at the end of the study. At baseline at weeks eight, 16 and 23, patients discontinued taking any neuropathic pain medications and completed the BPI within the following week, with precise timing based on individual patient analgesic requirements. Following pain medication withdrawal and BPI scoring, patients were able to remain without their chronic neuropathic pain medication regimens if they felt able to do so[14].

- **THE SHORT FORM (SF-36) QUESTIONNAIRE[31]**

The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

Appendix 2. Health Economic Review

Company submission - economic evidence

1.0 Description and critique of company submission

The company submission[13] describes an economic model developed from the methods used by Connock et al in a Health Technology Assessment of Enzyme Replacement Therapy (ERT) in Fabry disease, published in 2006[6]. The authors of the company submission identified a number of limitations and a range of assumptions in the Connock model that significantly favoured ERT versus the comparator of usual symptomatic care. The Connock model was run using agalsidase beta as the ERT. This was because agalsidase beta was considered less expensive than agalsidase alfa (annual cost for a 50kg patient was reported as £84,630 versus £86,294)[1]. In all other respects, the model assumptions would have been equally applicable with either agalsidase beta or agalsidase alfa.

The agalsidase alfa model presented in the company submission attempts to address some of the assumptions used in the Connock model. However, these adjustments relate primarily to the modelling of the disease state rather than the effectiveness of treatment. The most significant limitations and assumptions used in the Connock model, which are essential to the estimation of quality adjusted life years (QALYs) gained for ERT, still remain in the agalsidase alfa model as discussed in this Appendix.

The company has not provided the agalsidase alfa model; therefore verification of the model outputs is not possible.

2.0 Population

The agalsidase alfa model was designed to assess the cost-utility of the long-term use of agalsidase alfa as ERT in patients with Fabry disease, which reflects its licensed indication[1]. A hypothetical cohort of 1000 patients was simulated and followed until death. The Connock model simulated a birth cohort of male patients who were assumed to have an average weight of 50kg (assumed average weight across adults and children) and received treatment from birth until death[6]. The agalsidase alfa model[13] was reported to be have been adapted by applying a Welsh-specific male/female ratio to average male and female values where applicable. This is presumably to reflect the fact that females may also be affected by Fabry disease. However, no further details are provided and it is doubtful whether this adaptation captures the expected differences in disease experience and outcomes between male and female patients. Signs and symptoms are more variable and disease progress is slower in females than in males [4].

In addition, treatment was assumed to start at diagnosis in the agalsidase alfa model, rather than at birth. This was modelled by randomly sampling from a beta distribution with the mean age (± standard deviation) of diagnosis for patients entered into the Fabry Outcome Survey (FOS) disease registry database[32]. However, the figures presented (mean age 28.54; SD 16.46) results in a negative parameter of the beta distribution, making it invalid. Body weight was set at 50kg, as per the Connock model. Sampling for death hazards for individual patients was based on Welsh-specific demographic[13].

3.0 Perspective and time horizon

The model considers agalsidase alfa and usual care treatment costs from the perspective of NHS Wales[13]. No consideration is given to any personal and social service costs/resources, which could feasibly be substantial for a proportion of this patient group.

A lifetime horizon was chosen for the model[13], which is appropriate for this disease and its treatment.

4.0 Comparator

Defining the appropriate comparator group requires consideration of whether agalsidase alfa is likely to displace agalsidase beta, which is also licensed for the treatment of Fabry disease and was accepted for use in NHS Wales in April 2007[12]. If there is a possibility that patients who currently receive agalsidase beta will be transferred to agalsidase alfa, then agalsidase beta is the appropriate comparator. If, on the other hand, patients who are eligible for agalsidase alfa currently receive standard care, then standard care (labelled usual care in the company's submission) is the appropriate comparator.
The comparator used in the economic model for agalsidase alfa[13] is usual care, which includes treatment of co-morbidities. The Connock model, used to provide data in support of agalsidase beta in the submission to AWMSG, also used usual care as the comparator[6].
There are no direct comparative efficacy data for agalsidase alfa and agalsidase beta. The agalsidase alfa company submission considers the incremental cost effectiveness ratio (ICER) for agalsidase alfa versus usual care, calculated from the agalsidase alfa model, alongside the ICER for agalsidase beta versus usual care, as calculated in the Connock model.

5.0 Clinical inputs

None of the main clinical inputs of the agalsidase alfa model are derived directly from the clinical trial data for agalsidase alfa. Instead, utility values and mortality data have been largely obtained, or derived from other sources and assumptions made in their application.

5.1 Utility values

5.1.1 Untreated patients

The Connock model assumes that untreated patients have a utility value of 0.6 (based on the mid-point of the range of values in the published literature), which implies that the utility values are independent of the actual symptoms/complications experienced. However, the model included in the company submission attempts to estimate the impact of Fabry disease by calculating the individual lifetime risk of, and change in health utility resulting from, the most significant complications of the disease (Renal effects: haemodialysis, peritoneal dialysis, transplantation, graft rejection; Cerebrovascular effects: stroke, transient ischaemic attack; chronic pain; coronary heart disease; angiokeratoma).

Utility values for patients discharged from the Cardiff and Vale NHS Hospitals Trust after treatment for conditions that reflect the complications of Fabry disease (except pain) were obtained from data collected as part of the Health Outcomes Data Repository (HODaR) [33]. Regression analysis was used to estimate the relationship between age, occurrence of symptoms and quality of life.

For pain, the analysts refer to the use of a published model of the relationship between Brief Pain Inventory (BPI) scores and utility values, derived from FOS data on 20 patients who received agalsidase alfa for two years[34]. However, elsewhere in the submission, the authors note that the relationship between BPI scores and EQ-5D scores is unknown, and instead use regression analysis of data relating to the use of duloxetine for the treatment of painful diabetic neuropathy[35].

5.1.2 Treated patients

Both the Connock model and the agalsidase alfa model assume that ERT is 100% efficacious[6,13]. Fabry disease patients are assumed to have the same utility values as the age-matched general population whilst receiving ERT (i.e. they are assumed to gain immediate full health upon receiving ERT). Connock and colleagues note that this is

approach is optimistic[6] and this assumption biases the models in favour of ERT. The agalsidase alfa model uses Welsh-specific population norm data for EQ-5D scores[13].

5.1.3 Asymptomatic patients

Overall changes in health utility in asymptomatic patients are reported to have been estimated via age-dependent regression of quality of life based on HODaR data. The equation derived is provided and where the predicted value generated exceeded 1.0, the value was constrained to 1.0 (i.e. perfect quality of life). No further details are provided in terms of the HODaR data used, etc.

5.2 Risk of complications of Fabry disease

The lifetime risk of developing each of the Fabry disease complications in the agalsidase alfa model have been obtained from published data from the FOS database[32]. The pooled prevalence of each of the complications in 375 males and 396 females has been taken as the lifetime risk of developing each of the complications. It is unclear how reliable this estimation of lifetime risk is. Males and females appear to differ in their progression of disease and the signs and symptoms are more variable in females than in males[32]. One of the limitations of the Connock model was that the risks of individual complications were assumed to be independent, and a more realistic assumption would have been to use correlated risks. The company's agalsidase alfa model also has this limitation, with the exception of renal transplantation, which follows dialysis[13].

5.3 Mortality estimation

Both the Connock model[6] and the agalsidase alfa model[13] assume that patients who receive treatment with ERT become asymptomatic and have a normal life expectancy. These assumptions significantly bias the model in favour of ERT. For untreated patients, the scale parameter of the Weibull survival curves for the general Welsh population was adjusted to fit the life expectancy of patients with Fabry disease as used in the Connock model.

5.4 Adverse events

Adverse events associated with the use of agalsidase alfa are not considered in the economic model.

6.0 Healthcare resource utilisation and cost

The agalsidase alfa model considers the direct annual costs of Fabry disease complications (i.e. costs of usual care), which are taken from or calculated from a range of published sources (including the Connock model) and are reported to have been adjusted to 2006 prices using inflation rates taken from Medical Services Index 2007[13]. This approach is appropriate, although it is not possible to verify all the costs that have been assumed.

In the base-case analysis of both the Connock and the agalsidase alfa model, it is assumed that there is no wastage of ERT, i.e. complete vials are used. In the base-case analysis, the agalsidase alfa model uses the current BNF-listed cost of a 3.5ml vial of agalsidase alfa to estimate the annual cost of treating a 50kg patient (which would be equivalent to £86,288.06). In the company's submission, reference is made to the use of agalsidase alfa in routine practice, where doses are rounded up to the nearest vial one fortnight, and rounded down to the nearest vial the next. Although this minimises waste, it is not in accordance with the SPC.

One of the scenario analyses that have been performed explores the effect of drug wastage (see Section 9. Sensitivity Analysis).

No consideration is given to any personal and social service costs/resources, which is a limitation of the model as these could feasibly be substantial for a proportion of this patient group.

7.0 Discounting

All costs and outcomes were discounted at 3.5% in the base case analysis, which is the preferred discount rate. No other discount rates have been explored in sensitivity analyses.

8.0 Results

8.1 Base-case

The scenario modelled in the base-case analysis of the agalsidase alfa model[13] is the same as that modelled in the base-case analysis in the Connock model[6]: Patients have a mean weight of 50kg (assumed average weight across adults and children), regain full health when ERT is started, treatment is 100% effective and there is no drug wastage from the use of vials.

The ICER for agalsidase alfa versus usual care was estimated as £252,951 per QALY gained. This is based on additional costs of £887,858 and a gain of 3.51 QALYs versus usual care[13].

For comparison, the Connock model generated an ICER for agalsidase beta versus usual care of £252,112 per QALY gained. This is based on additional costs of £2,537,792 and a gain of 10.07 QALYs versus usual care[1].

There is a substantial difference in the absolute costs of treatment for usual care and ERT, and the absolute QALY gain with ERT versus usual care reported in each of the models. It is unknown whether the more comprehensive model of disease progression included in the company submission provides a closer approximation to the expected health gains and costs, than the Connock model.

It should be noted that ERT dosing (and, hence, cost) is based on body weight. The agalsidase alfa model simulates treatment started at the point of diagnosis. The mean weight of 50kg used in the base-case analysis may be lower than the mean weight of patients at diagnosis, which based on data in the FOS study [32] occurs at age 25 years+ (i.e. at adult weight). Body weight is explored in the sensitivity analysis.

8.2 Sub-group analysis

No sub-group analysis was conducted, which is unfortunate as this could potentially have been informative. For example, signs and symptoms are more variable and disease progress is slower in females than in males[32]. In addition, as a consequence of the natural history of Fabry disease, children may be relatively symptom-free compared with adult patients. Clinical trial data for agalsidase alfa use in children presented in the company submission indicates that the quality of life in the children involved in the trials may not have been significantly reduced from the norm[13]. Therefore, use of agalsidase alfa at an early age could be very influential on the ICER versus usual care, (e.g. the major costs of usual care, such as renal dialysis/transplantation, would occur later in life, but the costs of agalsidase alfa would begin early).

9.0 Sensitivity analysis

Probabilistic sensitivity analysis was not attempted. Three one-way sensitivity analyses were performed, but there appear to be several errors in the presentation and calculation of results.

9.1 Mean body weight adjusted

ERT dosing (and, hence, cost) is based on body weight. The mean body weight was adjusted to 70.39kg (SD:12.9) based on the mean weight of patients in the largest published trial of Fabrazyme®[13]. The ICER increased to £359,597 per QALY gained due to the increased cost of agalsidase alfa and no change in the QALYs gained versus usual care.

9.2 Drug wastage if recommended dose of 0.2mg/kg does not equate to whole number of vials

In this scenario, patients with a mean weight of 50kg are assumed to receive the exact dose of agalsidase alfa at each administration, with associated drug wastage (presumably based on the use of just the 3.5ml size vials). The company submission states that this increased the ICER to £274,837 per QALY gained. However, there appear to be some errors in the calculation and presentation of the results for this scenario as presented in the company submission (Appendix C, Table 8). The calculated ICER appears to be based on the cost of agalsidase alfa + usual care, rather than on the incremental cost over usual care, and the table incorrectly reports what the incremental cost would be.

It should be noted that a 50kg patient could receive the exact required dose without drug wastage if both the 3.5ml and 1.0ml vials are available, although the cost per mg is higher for the 1ml vial than the 3.5ml vial.

9.3 Treatment efficacy varied between individuals by random sampling in range 50–100%

The company presented a sensitivity analysis whereby efficacy was varied by random sampling from a uniform distribution of the range 50% to 100%. This, in effect, is identical to specifying efficacy as 75%.

Under this assumption, the ICER was reported as £323,839 per QALY gained. Again there are errors in this figure, as it appears to be based on the cost of agalsidase alfa + usual care, rather than on the incremental cost over usual care.

The cost of agalsidase alfa + usual care as presented for this sensitivity analysis is illogical as it is lower than that presented in the base-case analysis that assumed 100% efficacy. If efficacy was anything less than 100%, the costs of agalsidase alfa + usual care would at best stay the same as in the base-case analysis, but would logically increase compared with the base-case analysis (as the costs of agalsidase alfa would remain constant, but its lower efficacy would result in further usual care costs being incurred).

Company submission - budget impact analysis

1.0 Description and critique of company submission

The company submission includes a budget impact analysis that estimated the distribution of costs associated with agalsidase alfa over the next five years using a bootstrapping approach. The model was populated with data on the prevalence of Fabry disease and its complications, taken from a number of sources including a previous WMP assessment of agalsidase beta, FOS data, and UK-based costing studies where available. A total of 1000 cohorts of 30 patients with different baseline characteristics of weight, sex and symptoms/co-morbidities were simulated by random sampling.

The model required patients to by symptomatic. The probability of exclusion from treatment due to factors such as pregnancy, side effects, etc. was assumed to be 5% in the absence of any data. The base-case analysis uses the same assumptions around effectiveness, mean body weight and no drug wastage, as used in the cost-effectiveness model. Three

other scenarios are reported as sensitivity analyses, including variation in market share in one of the scenarios[13].

2.0 Perspective and time horizon
The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon.

3.0 Data sources
3.1 Incident cases
Data on incident cases is lacking. Therefore, the model mirrored the general changes expected in the Welsh population due to deaths, births and migration as calculated from Government Acturay's Department data, 2005. Over the five-year period considered in the model, patient numbers are expected to rise by 1.1%.

3.2 Prevalent and eligible cases
The company submission assumes there are 30 patients with Fabry disease in Wales. This is taken from the WMP assessment of agalsidase beta[11]. The prevalence is assumed to be 1:100,000 [11].

The base-case analysis assumes that 5% of symptomatic patients would be ineligible for treatment due to factors such as pregnancy, lactation, side effects, etc. No data are available to support or further inform this. The model assumes that all remaining symptomatic patients are eligible for ERT.

3.3 Market share
See section 5. Sensitivity analysis.

3.4 Rates of adoption
No analyses of differential rates of adoption are presented. The base-case scenario assumes 100% adoption from year one onwards.

3.5 Displaced medicine(s)
The analysis assumes, implicitly, that agalsidase alfa displaces agalsidase beta, as all 30 Fabry patients in Wales are treated with the former in the base-case scenario. The benefits of using agalsidase alfa instead of agalsidase beta have been described (e.g. shorter infusion time), but have not been considered in the budget impact model.

4.0 Results
4.1 Base-case
In the base-case analysis, the budget impact model estimates the cost of agalsidase alfa to be £2.43million in year one, increasing to £2.46million in year five due to a 1.1% net increase in the population size. This is based on a mean patient weight of 50kg, 100% effectiveness and no drug wastage.

The authors of the company submission suggest that ERT reduces the frequency and severity of symptoms and hence the costs of these. This reduction in costs of symptoms has not been quantified, but the authors suggest that the reduction in direct costs of symptoms could credibly be 50%, which would be equivalent to £35,000 across the 30 patients each year. This is based on assumptions.

4.2 Sub-group analysis
No sub-group analysis has been conducted.

5.0 Sensitivity analysis

Three further scenarios were modelled.

5.1 Mean body weight adjusted

As in the cost effectiveness model, the mean body weight of patients was adjusted to 70.39kg (SD:12.9) based on the mean weight of patients in the largest published trial of agalsidase beta[36]. This increased the agalsidase alfa treatment costs to £3.41million in year one, and to £3.45million in year five.

This scenario was also used to compare the budget impact of agalsidase alfa with that estimated for agalsidase beta in the WMP assessment of agalsidase beta[11]. In year one, the budget impact of agalsidase beta was estimated as £3.54million[11], leading the authors of the agalsidase alfa submission to suggest that treatment of all patients in Wales with agalsidase alfa instead of agalsidase beta could save £129,000 per year. However, as noted by the authors, the model designs are not directly comparable, and this comparison is not valid.

This scenario was also used to illustrate the effects of equal market share for agalsidase alfa and agalsidase beta[13]. The annual cost of equal market share in year one is calculated as £3.48million. However, this is still based on the annual cost of agalsidase beta as estimated by a different budget impact model.

5.2 Reduced efficacy

Treatment efficacy was randomly sampled over the interval 50%–100% (effectively resulting in an efficacy of 75%) for each simulation that was run. The agalsidase alfa treatment costs in year one were £2.45million, rising to £2.47million in year five, which is a marginal increase over the costs calculated in the base-case analysis.

5.3 Reduced efficacy, realistic distribution of body weight, and drug wastage assumed

This scenario explored the mixed effect of reduced efficacy (75%), randomly sampling body weight from a normal distribution with a mean of 70.39kg (SD:12.9), under the assumption of drug wastage. The agalsidase alfa treatment costs in year one were £3.84million, and increased to £3.88million in year five, i.e. 58% higher than in the costs estimated in the base-case analysis.

Appendix 3. Summary of Medical Expert Opinion

- NHS National Commissioning group have prepared guidelines for Fabry disease. There is no equivalent programme for patients in Wales and patients have variable clinical pathways.
- Cambridge, Manchester and London are all dedicated NSCAG centres. The current LSD service at University Hospital of Wales is likely to play a major role in the future.
- ERTs have led to spectacular advances in this disease area – not using them would be sub-optimal treatment.
- Current preferred treatment is Fabrazyme® as per the AWMSG advice. This medicine is broadly equivalent to Replagal®.
- Likely prevalence is a total of 20 patients with 10 receiving treatment in Wales.
- It would be appropriate for patients to continue their current ERT, but Replagal® would allow more complete commissioning for an All-Wales service.

Appendix 4. Patient Interest Group submission (provided as a separate document)

Appendix 5. Company written response (provided as a separate document)