SMC2591

pegunigalsidase alfa concentrate for solution for infusion (Elfabrio®)

Chiesi Ltd.

06 October 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent medicine process

pegunigalsidase alfa (Elfabrio®) is not recommended for use within NHSScotland.

Indication Under Review: for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry Disease (deficiency of alpha-galactosidase).

In a two-year, double-blind, randomised, phase III study, pegunigalsidase alfa appeared to have a similar annualised change in estimated glomerular filtration rate (eGFR) compared with an alternative enzyme replacement therapy.

The company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

The submitting company has indicated their intention to make a resubmission.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Pegunigalsidase alfa is a pegylated recombinant form of human alpha-galactosidase-A (GLA) and is an enzyme replacement therapy (ERT) that supplements or replaces the absent or reduced GLA enzyme that is the pathological cause of Fabry Disease.[1, 2] The recommended dose of pegunigalsidase alfa is 1mg/kg, administered by intravenous infusion, once every two weeks.[1]

1.2. Disease background

Fabry Disease is a rare, inherited, X-linked, lysosomal storage disorder that is caused by mutations in the GLA gene; this leads to the absence or reduction of the GLA enzyme, which has a key role in the metabolism of globotriaosylceramide (Gb3) from oligosaccharides, glycoproteins and glycolipids. The decreased activity of GLA results in the accumulation of Gb3 and its degradation product globotriaosylsphingosine (lyso-Gb3), which can lead to organ damage affecting the kidneys, heart, cerebrovascular system and nervous system with life-threatening complications. Fabry Disease is characterised by chronic pain, skin lesions, cardiac deficiencies and, in particular, renal involvement. [1, 2]

Fabry disease is categorised based on the age of symptom onset and the extent of organ involvement. The classic form of the disease occurs during childhood or adolescence, with progression to end-stage renal disease, cardiac complications, and/or cerebrovascular disease around 40 to 50 years of age. The non-classic (atypical) form occurs later in life and has a more variable disease course, with less severe complications that may only be limited to one organ. Since the disease is X-linked, it expresses itself differently in males and females, with females usually having milder symptoms than males.[1, 2]

1.3. Company proposed position

The submitting company has requested that pegunigalsidase alfa is restricted for use in adults with symptomatic Fabry Disease who would usually be offered an ERT.

1.4. Treatment pathway and relevant comparators

There is currently no cure for Fabry Disease and patients are treated on an individual basis.[2, 3] Treatment aims to delay or reverse progression, or stabilise clinical parameters.[3, 4] There are two classes of treatment; ERT (agalsidase alfa and agalsidase beta) and pharmacological chaperone (migalastat).[2, 3] For adult patients with Fabry Disease and who do not have a migalastat-amenable mutation, either of the ERTs (agalsidase alfa and agalsidase beta) are treatment options[2, 3]; both of these medicines predate SMC and are part of a risk-sharing scheme with National Services Scotland (NSS) for inherited metabolic disorder (IMD) medicines and a nationally commissioned service.[5, 6] Prescribing data shows the numbers of patients in NHS Scotland receiving agalsidase alfa and agalsidase beta are similar.

Treatment guidelines recommend migalastat for adult patients with a confirmed diagnosis of Fabry Disease with a migalastat-amenable mutation and who meet the treatment initiation criteria[3]; it is suggested that this would apply to approximately 30% of patients with Fabry Disease.[2] Migalastat was accepted for restricted use by SMC (dependent on enzyme activity levels) for the long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease and who have an amenable mutation (SMC1196/16).

The submitting company considered that only agalsidase alfa and agalsidase beta are relevant comparators in this submission as their proposed positioning for adult patients with symptomatic

Fabry Disease who would usually be treated for ERT would exclude those with a migalastat-amenable mutation.

1.5. Category for decision-making process

Eligibility for interim acceptance decision option

Pegunigalsidase alfa received an Innovation Passport allowing entry into the Medicines and Healthcare Products Regulatory Agency Innovative Licensing and Access Pathway.

Eligibility for a PACE meeting

Pegunigalsidase alfa meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support pegunigalsidase alfa comes from the BALANCE study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	BALANCE study[2, 7]
Study Design	International, randomised, double-blind, parallel group, phase III study.
Eligible Patients	• Symptomatic patients aged 18 to 60 years, with a confirmed diagnosis of Fabry Disease. • Screening eGFR of 40 to 120 mL/min/1.73m^2 as per the CKD-EPI equation.[a] • Screening linear eGFR slope less than -2 mL/min/1.73m^2 as per the CKD-EPI equation.[b] • No AKI in the past 12 months prior to screening. • UPCR >0.5 g/g and not treated with an ACE inhibitor or ARB. • Treatment with agalsidase beta 1mg/kg every 2 weeks for ≥ one year.[c]
Treatments and randomisation	Patients were randomised in a 2:1 ratio to either: switch to and receive pegunigalsidase alfa (n=52) or continue on agalsidase beta (n=25); both treatments were administered intravenously at a dose of 1mg/kg every 2 weeks, and were to continue for up to 2 years. Randomisation was stratified according to UPCR (less than or ≥ 1g/g). There was no treatment adjustment in the group of patients previously treated with agalsidase beta.
Primary outcome	The annualised change in eGFR slope, derived from eGFR assessments over time.
Selected Secondary outcomes[d]	• Change in urine and plasma lyso-Gb3 concentration. • Change in scores for pain severity and interference (measured on the short form BPI).[e] • Incidence of Fabry clinical events.[f]
Statistical analysis	The aim of the interim analysis (after 12 months) was to demonstrate that in terms of eGFR slope, pegunigalsidase alfa is non-inferior to agalsidase beta by a non-inferiority margin of 3.0 mL/min/1.73m^2/year. The original aim of the final analysis (after 24 months) was to demonstrate superiority of pegunigalsidase alfa over agalsidase beta. However, in January 2022, the submitting company modified the objective of the final analysis (after 24 months) from superiority to non-inferiority testing. The pre-planned non-inferiority margin from the interim analysis (12 months) was used for the final analysis (24 months); these were descriptive statistics only. Secondary outcomes were all descriptive only.

[a] However, no patients had an eGFR value of 91 to 120 mL/min/1.73m^2 and a historical eGFR value >120 mL/min/1.73m^2 (9 to 18 months before screening).
[b] based on at least three serum creatinine values over approximately 1 year (range 9 to 18 months, including the value obtained at screening visit).
[c] Patients were required to have received at least 80% of their scheduled infusions (10.4 out of 13 infusions) and been stable for the previous 6 months.
[d] recommended efficacy measures (with goals) in the British Inherited Metabolic Diseases Group (BIMDG) guidelines.[3]

[e] The Short Form BPI is designed to rapidly assess the severity of pain and its impact on functioning, and yields scores for "Pain at Its Worst in Last 24 Hours" (pain severity) and "pain on average" (pain interference). The scales are scored from 1 to 10, with a score of 1–4 points indicating mild pain, 5–6 indicating moderate, and 7–10 indicating severe.
[f] This was a composite outcome consisting of renal, cardiac, cerebrovascular events; as well as non-cardiac related deaths.

ACE = angiotensin converting enzyme; AKI = acute kidney injury; ARB = angiotensin receptor blocker; BPI = brief pain inventory; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; lyso-Gb3 = globotriaosylsphingosine; MRI = magnetic resonance imaging; UPCR = urine protein creatinine ratio

At the time of the interim analysis (after 12 months), considered by the European regulator as the primary analysis, the lower boundary of the 95% confidence interval for the difference between pegunigalsidase alfa and agalsidase beta was -3.03 mL/min/1.73m^2/year (below the non-inferiority margin of -3.0 mL/min/1.73m^2/year), and non-inferiority was not demonstrated at this timepoint.[1, 2]

As outlined in table 2.1, the submitting company changed its statistical approach for the final analysis of the primary outcome after 24 months from superiority to non-inferiority testing while the BALANCE study was ongoing. Using a regression model, the median eGFR slopes for pegunigalsidase alfa and agalsidase beta at 24 months appeared similar; the lower boundary of the 95% confidence interval for the difference between pegunigalsidase alfa and agalsidase beta was -2.44 mL/min/1.73m^2 (above the non-inferiority margin of -3.0 mL/min/1.73m^2/year).

However, non-inferiority over agalsidase beta was not demonstrated due to the lack of data to support the non-inferiority margin of 3.0 mL/min/1.73m^2/year for agalsidase beta.[2, 8]

Secondary outcomes appeared similar between the two treatment groups; however, some outcomes appeared to favour agalsidase beta over pegunigalsidase alfa, such as the change in urine lyso-Gb3 concentrations and the occurrence of Fabry Clinical Events (*see table 2.2 for further details*).

Table 2.2 Primary and selected secondary outcomes for the BALANCE study.[1, 2]

	Pegunigalsidase alfa (n=52)	**Agalsidase beta (n=25)**	**Difference (95% CI)**
Primary outcome: annualised change (slope) in eGFR (mL/min/1.73m^2/year) after 12 months of treatment (means of eGFR slopes using longitudinal mixed model)[a]			
Mean (range) eGFR slope (mL/min/1.73m^2/year) at baseline	-8.07 (-30.5 to 6.3)	-8.48 (-20.3 to -2.8)	-
Mean (95% CI) eGFR slope (mL/min/1.73m^2/year) after 12 months	-2.51 (-3.84 to -1.18)	-1.75 (-3.59 to 0.09)	-0.76 (-3.03 to 1.51)[b]
Annualised change (slope) in eGFR (mL/min/1.73m^2/year) after 24 months of treatment (medians of eGFR slopes using regression model)[c]			
Median eGFR slope (mL/min/1.73m^2/year) at baseline	-7.10	-8.21	-

Median (95% CI) eGFR slope (mL/min/1.73m^2/year) after 24 months	-2.51 (-3.79 to -1.24)	-2.16 (-3.81 to -0.51)	-0.36 (-2.44 to 1.73)[d]
Secondary outcome: Change in urine lyso-Gb3 concentrations after 24 months of treatment (pM/mM creatinine)			
Mean (SE) at baseline	48.1[e] (7.8)	44.5[f] (10.9)	-
Mean (SE) change from baseline at 24 months	7.0[g] (7.7)	-11.2[h] (4.7)	18.1 (0.1 to 36.1)[i]
Secondary outcome: Change in plasma lyso-Gb3 concentrations after 24 months of treatment (nM)			
Mean (SE) at baseline	26.2 (3.78)	32.1 (7.1)	-
Mean (SE) change from baseline at 24 months	3.30[j] (1.4)	-8.74[k] (4.9)	NR
Secondary outcome: Change in scores for pain severity and interference (measured on the short form BPI)[l]			
"Pain at its worst in the last 24 hours" (pain severity)			
Mean (SE) at baseline	3.5 (0.4)	2.6 (0.6)	-
Mean (SE) change from baseline at 24 months	-0.1[l] (0.5)	0.6[k] (0.6)	-0.7 (-2.2 to 0.8)
"Pain on average" (pain interference)			
Mean (SE) at baseline	2.2 (0.3)	2.2 (0.4)	-
Mean (SE) change from baseline at 24 months	0.4[l] (0.3)	0.2[k] (0.4)	0.2 (-0.9 to 1.2)
Secondary outcome: Occurrence of Fabry Clinical Events			
Overall FCEs, n (%)	9 (17.3)	2 (8.0)	NR
Number of events (rate per 100 patient years)	11 (11.2)	2 (4.0)	NR

[a] To demonstrate non-inferiority.
[b] Statistical non-inferiority was missed for the primary outcome since the lower 95% CI did not meet the pre-specified non-inferiority margin of -3 mL/min/1.73m^2/year.
[c] Originally planned to demonstrate superiority but changed to a non-inferiority analysis after agreement with another regulatory authority (descriptive statistics only).
[d] Non inferiority tests for the secondary outcomes could not formally be carried out under adequate control of the overall type-1 error, since statistical non-inferiority was missed for the primary outcome.
[e] n=48, assessed at baseline.
[f] n=22, assessed at baseline.
[g] n=37, assessed at 24 months.
[h] n= 19, assessed at 24 months.
[i] The confidence intervals at both post-baseline time points (months 12 and 24) did not contain 0, which suggests a difference in favour of agalsidase beta.
[j] n=46, assessed at 24 months.
[k] n=22, assessed at 24 months.
[l] n=45, assessed at 24 months.

CI = confidence interval; eGFR = estimated glomerular filtration rate; LVMI = left ventricular mass index; mM = millimolar; MRI = MRI = magnetic resonance imaging; nM = nanomolar; NR = not reported; pM= picomolar; SE = standard error.

2.2. Health-related quality of life outcomes

In the BALANCE study, Health Related Quality of Life (HRQoL) was assessed using the EuroQol 5 Dimensions 5 Levels Quality-of-life Questionnaire (EQ-5D-5L) questionnaire which includes domains on mobility, self-care, usual activities, pain/discomfort and anxiety/depression; these instruments were used at baseline and then every 6 months for 2 years. After 24 months, most patients reported improvement or no change in most of the domains, with either treatment. Results for the mobility and self-care domains were similar between the two groups. Worsening of usual activities (22% versus 9.1%) and anxiety/depression (15% versus 9.1%) were reported for more patients in the pegunigalsidase alfa group than the agalsidase beta group.[2]

2.3. Supportive studies

The submitting company provided supporting evidence from the 12-month, open-label, single-arm phase III study BRIDGE (n=22) in which all patients switched from prior agalsidase alfa. BRIDGE was primarily a safety study but efficacy was a secondary outcome. The mean annualised eGFR slope was -5.90 mL/min/1.73m^2 before switching and -1.19mL/min/1.73m^2 twelve months afterwards.[2] An integrated analysis of annualised eGFR slope was generated. This included data for the licensed 1mg/kg pegunigalsidase alfa dosing from the PB-102-F03 study (phase I/II), BALANCE, BRIDGE, and the follow-up study for BALANCE (PB-102-F60); this was compared with originally naïve patients (PB-102-F03). Only patients with at least 18 months of exposure were included, and this covered treatment of up to 7.6 years (for 1mg/kg every 2 weeks).[2]

The mean eGFR slope was -2.80 mL/min/1.73 m²/year in the overall population, as well as in the 1 mg/kg every 2 weeks dosing, and -2.56 mL/min/1.73 m²/year in previously untreated patients. In further analyses, most patients maintained normal or near normal left ventricular mass index (LVMI) values throughout the studies; mean changes were small and did not suggest deterioration of LVMI values over treatment. The severity of Fabry disease signs and symptoms according to the Mainz Severity Score Index and average pain severity remained stable in the switch studies.[2]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

A naïve indirect comparison between the phase III studies (BALANCE, BRIDGE, and BRIGHT) was conducted using data from the BALANCE (impaired renal function population), BRIDGE and BRIGHT studies to determine any differences in efficacy of pegunigalsidase alfa every 2 weeks for seven clinical outcomes across these studies. The results of the indirect comparison were not used in the economic evaluation.

3. Summary of Safety Evidence

A regulatory authority concluded that the clinical safety profile of pegunigalsidase alfa is overall comparable to that of other authorised ERTs for Fabry disease.[2]

Comparative safety data are only available against agalsidase beta from the BALANCE study. The cumulative exposure of treatment in the pegunigalsidase alfa group was 1,176.2 months and in the agalsidase beta group was 596.4 months. Any treatment-emergent adverse event (TEAE) was reported by 90% (47/52) of patients in the pegunigalsidase alfa group and 96% (24/25) in the agalsidase beta group; these were considered treatment-related in 40% (21/52) and 44% (11/25) of patients respectively. In the pegunigalsidase alfa and agalsidase beta groups respectively, patients reporting at least one treatment-related severe TEAE were 6.9% (2/52) versus 5.6% (1/25), and patients with a reported serious TEAE that was treatment-related were 3.4% (1/52)

versus 0%. Patients discontinuing therapy due to a TEAE was 3.8% versus 0%; none of these were serious.[2]

In a pooled safety analysis using data from the 111 patients who received the 1mg/kg dose of pegunigalsidase alfa, the most common TEAEs (>10% of patients) were nasopharyngitis (23%), headache (22%), diarrhoea (19%), back pain (19%), upper respiratory tract infection (14%), arthralgia (14%), pain in extremity (14%), dizziness (14%), nausea (13%), abdominal pain (12%), and vomiting (12%). The most commonly reported treatment-related adverse events were infusion-related reactions (IRRs), which occurred in 23% (26/111) of patients; 4.5% (5/111) of patients experienced serious IRRs, four of which were indicative of hypersensitivity reactions (these occurred during the first infusion of pegunigalsidase alfa).[2]

In the BALANCE study, in the pegunigalsidase alfa (n=52) and agalsidase beta (n=25) groups respectively, the number of patients with at least one IRR: within 2 hours of infusion were 21% and 24%; and within 24 hours of infusion were 33% and 32%. IRRs are more common in patients with a positive or induced anti-drug antibody (ADA) status. This is highlighted by the results of the pooled analysis where 37% (10/27) of the patients with a positive anti-drug antibody (ADA) status and 35% (6/17) of the patients with induced ADAs experienced IRRs, which contrasts to the proportion with a negative ADA status (13% [8/63]).[2] However, the regulatory authority highlighted that these appeared to be manageable with pre-medication, and noted that a 26% of patients at baseline already had a positive ADA status for pegunigalsidase alfa. It is also noted that the proportion of patients with neutralising ADA among those who have ADA was rather high (overall 90% or more).[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the phase III BALANCE study in patients with symptomatic Fabry Disease and renal impairment, the annualised change (slope) in eGFR was similar with pegunigalsidase alfa and agalsidase beta at 12 and 24 months.[1, 2]
- Pegunigalsidase alfa appeared to have a beneficial effect on secondary outcomes including plasma lyso-Gb3 levels[2]; reductions in plasma lyso-Gb3 have been reported to be indicative of ERT efficacy and are listed as a recommended clinical outcome by the BIMDG.[2, 3]
- Home infusion of pegunigalsidase alfa was allowed in all the studies, based on investigator's judgement. 65% (72/111) of patients in the pooled safety analysis received at least one dose of pegunigalsidase alfa treatment at home.[2]

4.2. Key uncertainties

- Regulatory authorities concluded that the limitations with the study design, including the small sample size (n=77), meant the results of the BALANCE study did not conclusively show that pegunigalsidase was at least as effective as agalsidase beta.[1, 2, 8] They considered the study design was inadequate to test the non-inferiority of pegunigalsidase alfa against agalsidase beta and did not allow to the size of the treatment effect of pegunigalsidase alfa to be clearly quantified.[2, 8]

- The BALANCE study assessed efficacy in patients with Fabry-related renal disease. However there is a lack of comparative evidence for patients with Fabry-related cardiac complications, since only 12/52 (pegunigalsidase alfa) and 9/25 patients (agalsidase beta) in BALANCE had hypertrophy at baseline.[2]
- The submitting company has requested that pegunigalsidase alfa is restricted for use in adults with symptomatic Fabry Disease who would usually be offered an ERT. However, BALANCE was conducted with a population who had renal impairment, and although the single-arm BRIGHT and BRIDGE studies were carried out in patients without renal impairment, further data is needed in this population. There is limited evidence in ERT-naïve patients, since all the phase III studies (BALANCE, BRIGHT, and BRIDGE) enrolled patients receiving prior ERT. There is also limited evidence in patients with amenable mutations who would be unsuitable for migalastat treatment but eligible for ERT (for example those with issues with adherence, tolerance, patient or clinician choice).
- In the BALANCE study, there was a significantly larger proportion of males in the agalsidase beta group (72%) compared with the pegunigalsidase alfa group (56%); given Fabry Disease is expressed differently in males and females, with females usually having milder symptoms, then this imbalance may bias in favour of pegunigalsidase alfa. In addition, differences in baseline characteristics suggested there was a higher proportion of patients with more severe Fabry Disease in the agalsidase beta group as well as differences in use of pre-medication at baseline, leading to uncertainty in the relative safety profile of pegunigalsidase alfa. [2]
- There is no direct head-to-head comparison with agalsidase alfa. The submitting company have assumed that agalsidase alfa and agalsidase beta are equivalent. They submitted evidence from an independent international retrospective cohort study of 387 patients (192 females) which found no difference in Fabry clinical events or eGFR slope in patients treated with agalsidase alfa or beta, with a median follow-up of 4.9 years (range: 0.8 to 14.4 years).[9] However, this assumption still remains an uncertainty.

4.3. Innovative Licensing and Access Pathway (ILAP) and ongoing studies

There are no efficacy data awaited from ongoing studies that are likely to address the uncertainties in the clinical evidence.

4.4. Clinical expert input

Clinical experts consulted by SMC noted that other ERTs are currently used and that pegunigalsidase alfa would offer an alternative treatment option.

4.5. Service implications

Clinical experts consulted by SMC did not anticipate any service implications however patients already on ERT would require to attend hospital for infusions when switching treatments.[1]

5. Patient and Clinician engagement PACE

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **pegunigalsidase alfa (Elfabrio®),** as an **orphan equivalent** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Fabry disease is a progressive, heterogeneous, multi-system, potentially life-limiting, lysosomal

storage disease that particularly affects the heart, kidney and nervous system. The symptoms of the disease and treatment burdens have a significant negative impact on the physical, financial, emotional and mental wellbeing of patients.

- Current therapies (enzyme replacement therapies: agalsidase alfa or agalsidase beta; and pharmacological chaperone: migalastat) slow disease progression. However, their effect is limited in those diagnosed late with established disease; and these have limited impact on pain, strokes and renal disease, especially when there is established kidney disease on diagnosis. There is an unmet need for more effective and tolerable treatment options.
- It is suspected that the pharmacological design of pegunigalsidase alfa, that is its PEGylation, may help deliver superior clearance of glycosphingolipids (by maintaining enzyme stability, prolonging plasma half-life and improving distribution of the active compound to key tissues) and may further slow progression of Fabry Disease, with particular benefit to the kidney. However, evidence to support these assumptions is from preclinical testing and surrogate endpoints and no improvement has yet been demonstrated on hard clinical renal outcomes.
- Although uncertain, due to an increased plasma half-life, there may be the potential for a longer time between infusions (for example 4 weeks) for some patients, which would reduce the burden on patients, their family and/or carers.
- There may be a short-term service impact in relation to treatment switch, but also the potential for longer-term benefits for services with potentially reduced infusions related reactions.
- An additional treatment option would be highly valued by the patient's family and caregivers, benefiting their family life, work/education, and societal engagement.

Additional Patient and Carer Involvement

We received a patient group submission from The MPS Society, which is a registered charity. The MPS Society has received 14% pharmaceutical company funding in the past two years, including from the submitting company. A representative from The MPS Society participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-minimisation analysis (CMA)
Time horizon	Lifetime (60 years)
Population	Adults with Fabry disease (FD) who would usually be treated with an ERT.
Comparators	Pegunigalsidase alfa was compared with agalsidase alfa and agalsidase beta.
Model description	The economic analysis used a Markov cohort state-transition model with ten health states: • Pain: neuropathic pain in the extremities. • Other symptoms: clinical signs and/or symptoms of left ventricular hypertrophy, chronic kidney disease (CKD) Stages 1–4 or white matter lesions. • End-stage renal disease (ESRD): CKD Stage 5 or kidney transplant.

	• Cardiac complications: atrial fibrillation, any other rhythm disturbance needing hospitalisation, a pacemaker or an implantable cardiac defibrillator (ICD) implantation, cardiac congestion for which hospital admittance was needed, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft. • Stroke: as diagnosed by a neurologist. • ESRD and cardiac complications. • Cardiac complications and stroke. • ESRD and stroke. • ESRD, cardiac complications and stroke. • Death. A cycle length of one year with a half-cycle correction was applied with patients entering the model at the age of 40 years. The model adopts an NHS Scotland and social care perspective. Transition probabilities were equal across treatment arms.
Clinical data	The primary source of clinical data for pegunigalsidase alfa in the economic model was the BALANCE study.[2] Other clinical data came from the previous NICE submission for migalastat[11], Waldek *et al*.[12], and clinical opinions. The company assumed equal efficacy between the two comparators agalsidase alfa and agalsidase beta. The company had not used discontinuation rates from the BALANCE study, but had instead used values much lower biasing the results in favour of pegunigalsidase alfa.
Extrapolation	The company did no extrapolation of health effects, but instead used transition probabilities from Rombach *et al* to move patients through the various health states of the model over time.[13]
Quality of life	No utility values were used as the cost-minimisation analysis assumed equal efficacy between treatment arms.
Costs and resource use	The economic analysis included costs associated with medicine acquisition, administration, health-state events, management of long-term comorbidities, follow-up visits and general healthcare resource use costs. Adverse events were assumed equal across the arms, but a scenario analysis was provided where they were included. All costs, other than the medicine acquisition and administration costs were equal across treatment arms. The submitting company applied a pragmatic dosage approach in the base case analysis where the dosage is rounded up or down to the nearest vial in order to minimise wastage, rather than dosing patients strictly to the dose specified for their weight.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

Base case results are presented in Table 6.2 below incorporating pegunigalsidase alfa at PAS price and list prices for comparator medicines.

The results are presented with pegunigalsidase alfa versus agalsidase alfa, agalsidase beta and a blended comparator. The blended comparator is a weighted average of 30% and 70% of the two comparators (agalsidase alfa and agalsidase beta respectively).

As clinical outcomes in both model arms were assumed equal, the main driver of the cost difference was the medicine acquisition cost, with some small cost savings for treatment administration for pegunigalsidase alfa compared to agalsidase beta.

When the PAS was taken into account, pegunigalsidase alfa became a cost-effective treatment option.

Table 6.2: Base case cost-effectiveness results (with pegunigalsidase alfa PAS, list price for all other medicines)

Costs	Agalsidase alfa	Agalsidase beta	Blended comparator
Incremental costs pegunigalsidase alfa versus comparator*	-£506,948	-£645,596	-£548,543
Key: PAS, patient access scheme. * A negative value indicates pegunigalsidase alfa is cost saving against the comparator			

6.3. Sensitivity analyses

A number of sensitivity analyses were provided, and the key scenarios are summarised in Table 6.3. The scenarios with the largest impact on the cost-savings in the cost-minimisation analysis were changes in discounting, time horizon and wastage. Additional scenarios provided upon request and showed that the cost-effectiveness of pegunigalsidase alfa compared to the comparators worsened when assuming higher rates of discontinuation from the BALANCE study combined with life expectancy calibrated to Waldek et al data. These were preferred as a base case as they represented the disease population and effects of pegunigalsidase alfa better.

Table 6.3 Scenario analyses results (with pegunigalsidase alfa PAS, list price for all other medicines)

No.	Scenario analysis	Scenario description	Incremental costs (pegunigalsidase alfa vs)*	
			Agalsidase alfa	Agalsidase beta
Base case			-£506,948	-£645,596
1	Time horizon	40 years	-£489,579	-£623,486
2		10 years	-£235,613	-£300,211
3	Wastage	No wastage	-£507,491	-£644,209
4		Full	-£535,873	-£489,599
5	AE management	Include AE management costs	-£507,169	-£645,817
* a negative value indicates pegunigalsidase alfa is cost saving against the comparator				

6.4. Key strengths

- The submitting company provided adequate sensitivity analyses with the exception of discontinuation rates explored.

6.5. Key uncertainties

- The BALANCE study did not achieve the primary outcome, and two regulatory authorities concluded there was inconclusive evidence of non-inferiority between pegunigalsidase alfa and agalsidase beta. As a cost-minimisation approach is used where outcomes are assumed equivalent between treatments on the basis of the BALANCE study; there is therefore

uncertainty associated with the economic evaluation and its base case finding of cost-savings for pegunigalsidase alfa.

- The discontinuation rates from the BALANCE study were not applied in the base case. Much lower values were applied, biasing the results in favour of pegunigalsidase alfa. Sensitivity analysis using the various rates from BALANCE were provided as noted. While it is acknowledged that the rates of discontinuation in clinical practice may not correspond to trial rates, the analysis did show the results were sensitive to varying the assumed rate.
- Given the uncertainty with the non-inferiority assumption of pegunigalsidase alfa against agalsidase beta, it may have been more appropriate for the submitting company to present a cost-utility analysis as the base case (it was provided as a scenario). The company did also provide some threshold analysis to indicate the level of QALY loss that would need to arise for pegunigalsidase alfa not to be cost-effective.
- The time horizon and mortality ratio used in the model base case does not reflect the reduced life expectancy of the patient population. The life expectancy from Waldek *et al*. better reflects the patient population.
- Prescribing data confirmed that the numbers of patients in NHS Scotland receiving agalsidase alfa and agalsidase beta are similar. The submitting company did provide some revised analysis using a 50:50 split for the blended comparator, combined with the preferred life expectancy projections from Waldek et al, which was helpful, with this usage being considered a better base case assumption for the blended comparator. The cost minimisation analysis result with these data was -£488,194 with PAS.
- The transition probabilities used in the model were taken from a study conducted in the Netherlands with a patient population of a different demographic and one of the original health states were removed for the submission. There may be issues with generalisability of the model from which the transition probabilities were taken, but as patients were assumed to move through the health states of the model in an identical way between the treatment and comparators, using alternative sources would still result in a cost-minimising result.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of pegunigalsidase alfa in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as pegunigalsidase alfa is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept pegunigalsidase alfa for restricted use in NHSScotland.

8. Guidelines and Protocols

In 2020, the British Inherited Metabolic Diseases Group (BIMDG) published guidelines for the treatment of Fabry Disease.[3]

In 2015, the European Fabry Working Group consensus document was published which had recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease.[4]

9. Additional Information

9.1. Product availability date

01 November 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Pegunigalsidase alfa 20mg/10mL solution for infusion (Based on full 20mg vial)	**1mg/kg every 2 weeks**	**130,540**

Costs from the submitting company NPAF on 04 July 2023. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration. Average weight of 70kg used.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish budget impact information due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 August 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:
No part of this advice may be used without the whole of the advice being quoted in full.
This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.