NICE National Institute for Health and Care Excellence

NICE guidance

Migalastat for treating Fabry disease

Highly specialised technologies guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Migalastat is recommended, within its marketing authorisation, as an option for treating Fabry disease in people over 16 years of age with an amenable mutation, only if migalastat is provided with the discount agreed in the patient access scheme, and only if enzyme replacement therapy (ERT) would otherwise be offered. Criteria for starting and stopping ERT for Fabry disease are described in the UK adult Fabry disease standard operating procedures (Hughes et al. 2013). With the discount provided in the patient access scheme, migalastat has a lower total cost than ERT, and potentially provides greater health benefits than ERT.

1.2 The committee noted that there were important limitations and uncertainties in the evidence presented for migalastat, and that NICE has not evaluated ERT (agalsidase alfa and agalsidase beta) for treating Fabry disease. It encourages the company, NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits of migalastat and ERT for treating Fabry disease, which should inform a future evaluation of the costs and benefits of all treatment options for Fabry disease.

2 The condition

2.1 Fabry disease is an inherited lysosomal storage disease caused by a non-functional or only partially functional enzyme, alpha-galactosidase A (alpha-gal A). Decreased activity of alpha-gal A in lysosomes results in the accumulation of enzyme substrates (Gb3 and lyso-Gb3) which cause cellular damage in tissues throughout the body.

2.2 Symptoms include pain that spreads through the body (called a Fabry crisis), gastrointestinal complications, headaches, impaired sweating, vertigo and hearing impairment. The age of onset, severity and progression of Fabry disease is variable. Accumulation of Gb3 in lysosomes leads to irreversible organ damage, resulting in progressive kidney and heart disease and increased risk of stroke at a relatively young age. Fabry disease can have a profound impact on health-related quality of life and can reduce life expectancy. The company estimates that there are 855 people with Fabry disease in England, suggesting a prevalence of approximately 0.002%. The company estimated that there are around 142 people for whom migalastat may be an appropriate option.

2.3 There is no cure for Fabry disease. Current treatment options are infusions with enzyme replacement therapy (ERT; agalsidase alfa or agalsidase beta) every 2 weeks, or supportive care to manage the symptoms and complications. ERT is a lifelong treatment that reduces symptoms and slows disease progression. In England, 8 highly specialist lysosomal storage disorder centres (5 adult centres and 3 paediatric centres) diagnose, assess and treat patients.

3 The technology

3.1 Migalastat (Galafold, Amicus Therapeutics) is an oral, small molecule drug designed to bind to the alpha-galactosidase A (alpha-gal A) enzyme as it is made, helping it to fold correctly and improving its function. Mutations that produce a form of alpha-gal A which responds to migalastat binding with a significant increase in function are known as amenable mutations. Amenability for migalastat is determined by checking the results of standard genetic testing against the migalastat amenability table: a list of all known amenable mutations compiled and kept up to date by the company as part of its marketing authorisation. Migalastat is a lifelong treatment and has a marketing authorisation in the UK for 'long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (alpha-galactosidase A deficiency) and who have an amenable mutation'.

3.2 The summary of product characteristics lists adverse reactions for migalastat including: headache, gastrointestinal disorders, skin rash and itching, depression, palpitations, muscle spasms, pain, tiredness, vertigo, shortness of breath, nosebleeds, weight gain, paraesthesia, proteinuria and increased creatine phosphokinase levels. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 The list price of migalastat is £16,153.85 per pack of 14 capsules (excluding VAT; company's evidence submission). The annual cost of treatment is £210,000 per patient (excluding VAT). The company has agreed a patient access scheme, in which migalastat would be provided with a discount. The discount is commercial in confidence and cannot be reported here. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

4 Evidence submissions

The evaluation committee (section 8) considered evidence submitted by Amicus Therapeutics, a review of this submission by the evidence review group (ERG) and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

4.1 Patient experts and patient groups highlighted the substantial impact of Fabry disease on people with the condition and their families.

- Fabry disease leads to progressive disability from transient ischaemic attacks, strokes, cardiac and renal disease.
- Adults may need dialysis, a kidney transplant or pacemakers and may be physically and mentally disabled.
- Symptoms in adults include hearing impairment, skin rash, gastrointestinal problems and fatigue. For children, symptoms include low energy, fatigue, pain and gastrointestinal problems.
- The effects of the disease can disrupt daily activities and cause absences from work or school.
- Symptoms generally appear in childhood but usually go unrecognised until adulthood, when organ damage has already occurred.
- People with Fabry disease may need a carer relatively early in life; often this responsibility is taken on by family members.
- Many people with Fabry disease have had psychological difficulties coming to terms with a lifelong progressive disorder, particularly before the introduction of enzyme replacement therapy (ERT) in 2001.
- ERT has a number of benefits but it also has limitations. The infusion dosage schedule of every 2 weeks means that people with Fabry disease cannot plan trips away from home. ERT must be kept refrigerated and there are risks of developing an infusion-related infection and antibodies to treatment. There

is also a possible need for a homecare nurse or carer to help with administration.

Clinical evidence

4.2 The company submitted evidence from 2 randomised controlled trials (ATTRACT and FACETS) and 2 open-label extension studies. ATTRACT was an 18-month open-label randomised controlled trial designed to show comparable effectiveness between migalastat and ERT. FACETS was a 6-month double-blind randomised controlled trial, in which patients who had not had treatment before had either migalastat or placebo.

4.3 The final outcomes reported in ATTRACT and FACETS can be grouped into renal function, cardiac function, health-related quality of life and safety outcomes. These outcomes were designed to capture aspects of Fabry disease morbidity that reflect how patients feel or that are used in clinical decision-making. The trials also reported biochemical outcomes of Gb3 and plasma lyso-Gb3 distributions and activity of the enzyme alpha-galactosidase A (alpha-gal A). These are primarily indicators of migalastat efficacy, but may not directly reflect patients' symptoms and do not themselves have a clear role in clinical decision-making.

4.4 Intention-to-treat (ITT) analyses were done based on all randomised patients in each trial. However, the ITT population included some patients who had mutations that were later found not to be amenable to migalastat. This was because the assay used to determine the amenability of mutations was changed to conform to GLP laboratory standards; the updated assay is the one referred to in the marketing authorisation for migalastat. Therefore the company used 'modified ITT' analyses which excluded these patients. In ATTRACT, the modified ITT population excluded patients with other protocol violations as well as non-amenable mutations and was effectively a per-protocol population. The ERG stated that 'modified ITT' is therefore potentially misleading (and has a different meaning in the 2 randomised controlled trials).

4.5 The small sample size (n=60) in ATTRACT made a standard non-inferiority

analysis impossible and the company presented its own pre-specified criteria for comparability. Based on these criteria, migalastat would be considered comparable to ERT if the difference between their means for the annualised change in glomerular filtration rate was 2.2 ml/min/1.73 m^2/year or less, and the overlap in the 95% confidence intervals for these means was greater than 50%.

4.6 In ATTRACT the pre-specified criteria for comparability of migalastat and ERT were met for both the co-primary outcomes of measured and estimated glomerular filtration rate. In FACETS, the change in glomerular filtration rate was measured at 6 months, although the company stated that this is generally considered too short to show a reliable trend.

4.7 In ATTRACT at 18 months, people who switched from ERT to migalastat had a statistically significant decrease from baseline in left ventricular mass index (LVMi; $p<0.05$), whereas in people who remained on ERT this decrease was not statistically significant. However, there was no statistically significant difference in the change from baseline between the groups. Patients in FACETS who continued into the open-label extension study had LVMi recorded after 18 or 24 months of migalastat; in patients who had migalastat for 24 months, a significant decrease in LVMi from baseline was seen.

4.8 ATTRACT included a composite clinical outcome of the rates of pre-specified renal, cardiac and cerebrovascular events and mortality over 18 months. The proportion of patients who had a renal, cardiac or cerebrovascular event was 29% (10/34) of patients who switched from ERT to migalastat compared with 44% (8/18) of patients who remained on ERT. Overall, renal events were the most common, followed by cardiac events. No deaths occurred.

4.9 Both ATTRACT and FACETS assessed health-related quality of life using the SF-36 health questionnaire physical component summary and the Brief Pain Inventory short form. ATTRACT also included the SF-36 mental component summary, and FACETS used the Gastrointestinal Symptoms Rating Scale. For ATTRACT, the company stated that SF-36 scores were comparable in the migalastat and ERT groups at baseline and there was little change in these scores over the 18-month study period. The Brief Pain Inventory pain severity component showed that patients had mild pain at baseline, and this did not change over the 18-month treatment period. For patients from FACETS continuing

in the open-label extension studies, the company reported changes in scores for the same Gastrointestinal Symptoms Rating Scale domains. After 18 or 24 months of migalastat, patients had statistically significant improvements in diarrhoea and indigestion compared with baseline. The company stated that there was a trend for improved reflux and constipation, although symptoms of abdominal pain remained stable. The company reported that SF-36 results were stable at 24 months. The company also stated that Brief Pain Inventory severity component scores did not change from baseline to month 24. Patients having migalastat reported stabilised cardiac symptoms and kidney function, improved mood swings and freedom from their infusion routine.

4.10 The company provided adverse event data from ATTRACT, FACETS and the open-label extension studies. In ATTRACT, between 94% and 95% of patients had a treatment-emergent adverse event, as did 91% of patients in FACETS. Nasopharyngitis and headache were the most common adverse events.

Economic evidence

4.11 The company submitted a Markov state transition model to estimate the costs and health effects of migalastat compared with ERT in people with Fabry disease. The 10 health states in the model represented the progression of Fabry disease over time. All health states were divided into incident (acute events) and prevalent (long-term). The model took the perspective of the NHS and Personal Social Services. It had a lifetime (52-year) time horizon, and a cycle length of 1 year. Costs and benefits were discounted at a rate of 3.5% per year.

4.12 The model structure and the values for transition probabilities between disease states were based on a Dutch study done in a group with Fabry disease. It was assumed that this was equivalent to a UK Fabry population. A number of structural assumptions were made in the company's model:

- ERTs are equivalent and can be grouped as a 'blended comparator'
- migalastat is clinically equivalent to ERT
- people having migalastat continue treatment until death, whereas some people having ERT stop treatment

- treatment adherence is 100%
- transition probabilities do not vary over time
- people cannot develop 2 complications in 1 model cycle (1 year)
- people with Fabry disease have a similar body weight to the UK general population
- about 50% of people self-administer ERT; for the remainder treatment is given by a nurse at home.

4.13 The starting distribution of people in the 5 health states was based on the baseline measurements of the ATTRACT trial population. The company stated that this population is representative of people with Fabry disease in England.

4.14 The company also provided details of the agreed patient access scheme, in which migalastat would be provided with a discount. The discount is commercial in confidence and so cannot be reported here. Estimates for costs associated with each health state were provided, including diagnostic, laboratory and imaging tests, primary and secondary care appointments, hospitalisations and treating complications. The costs were derived from NHS reference costs and Personal Social Services Research Unit (PSSRU) data. The frequency of diagnostic, laboratory and imaging tests for all people with Fabry disease was taken from the adult Fabry disease standard operating procedure, with the unit costs taken from the NHS reference costs. The costs for treating adverse events were also considered for each specific adverse event. The costs ranged from £0.06 (headache) to £47.28 (influenza), and were taken from the British national formulary and PSSRU.

4.15 The model captured health-related quality of life by assigning utility scores to each health state. The utility scores were taken from the Dutch study and described the health-state utility scores (disutility) for the complication states. Infusion-related utility decrements (disutilities) were based on a discrete choice experiment done by the company with 506 people from the UK general population.

4.16 The results of the company's cost–consequence analysis were presented as

costs, life years, and quality-adjusted life years (QALYs). Treatment with ERT is associated with 13.36 QALYs and migalastat with 14.33 QALYs, giving an incremental QALY gain of 0.98 for migalastat. The total and incremental costs of migalastat and ERT are confidential and so cannot be reported here. Because equivalent efficacy was assumed between migalastat and ERT, the infusion disutilities were responsible for virtually all (0.97 of 0.98 QALYs) of the differences between migalastat and ERT.

4.17 The company explored uncertainty in the economic model through deterministic and probabilistic sensitivity analyses and scenario analyses. The scenario analyses explored assumptions including ERT price discounts, utility scores, effectiveness of ERT and migalastat, patient demographics, perspective of the model, the time horizon, and ERT market share.

4.18 The company did a budget impact analysis, in which it estimated that there are 142 people with Fabry disease in the UK for whom migalastat may be considered. This estimate took into account the proportion of people with Fabry disease who have amenable mutations, which was assumed to be 40%. The number of people eligible for migalastat was predicted to increase by 1 person per year. An average body weight of 77.6 kg was used to calculate the ERT doses. The estimated budget impact of migalastat, taking into account the patient access scheme and confidential price discounts for ERT, is commercial in confidence and cannot be reported here.

Evidence review group review

4.19 The ERG stated that the studies providing clinical effectiveness evidence for migalastat are limited and there are concerns about the design of both pivotal randomised controlled trials and the related open-label extension studies. These concerns included:

- small populations and short trial durations
- imbalances in patient baseline characteristics between the trial arms in both randomised controlled trials and
- uncertainty as to how long individual patients had received migalastat

because it was not reported how many patients were recruited to the open-label extension study from each arm of FACETS.

One of the ERG's major concerns about the clinical evidence was the uncertainty in the comparability of migalastat and ERT. The pre-specified criteria for non-inferiority allowed a claim of comparability despite very wide confidence intervals for the outcome measures. The ERG was satisfied that the company's adverse event data did not raise any safety concerns over the use of migalastat.

4.20 The ERG noted a number of limitations in the company's economic modelling. The Markov model simplified Fabry disease progression. It did not allow people with end-stage renal disease to have kidney transplants and did not capture different levels of chronic kidney disease, different severities of stroke, or different types of cardiac complications. The ERG also noted that the probability of transition between these disease states remained constant throughout the patient's life; this was considered to be improbable and likely to underestimate the disease state transition probability. The model did not allow for poor adherence or for stopping migalastat at any point. The starting weight of people entering the model was a general population average; the ERG noted uncertainty about whether this was representative of people with Fabry disease. The ERG also noted uncertainty about whether people recruited to ATTRACT were representative of the Fabry population because the trial did not recruit people with severe manifestations of Fabry disease. The mortality rates used by the company led to an overestimation of life expectancy in the model. The ERG noted that the disutility associated with ERT infusion (−0.05) was high and was much greater than the disutility used in the model for developing a new disease complication (−0.018). This infusion disutility was calculated using the results of a discrete choice experiment done in healthy people; the ERG noted uncertainty about the comparability of these values with those of disease complications given the differences in the methods used for estimation.

4.21 The ERG did scenario analyses to address flaws and uncertainties in the model. These included:

- changing the price of ERT
- changing the proportions of people starting in each disease state (taken from

the Fabry registry)

- increasing the starting age
- including background mortality data from the Office for National Statistics life tables
- reducing patient body weight to reflect the average from ATTRACT
- calibrating transition probabilities to give a life expectancy of 66.5 years
- making discontinuation of migalastat and ERT equal in the model and including discontinuation of migalastat in people with end-stage renal disease
- reducing health-state utilities (taken from alternative sources) and
- reducing the disutility for infusion.

The ERG combined these assumptions into its preferred analysis, which resulted in an incremental QALY gain for migalastat of 0.34 compared with ERT.

4.22 The ERG noted that most transition probabilities between the model health states in the company's model did not vary with age, which led to an overestimate of the life expectancy of people with Fabry disease. The ERG stated that its analyses showed the potential effect of these uncertainties, but did not resolve them. The set of assumptions used in the ERG analyses was more conservative because it produced life expectancy estimates that are closer to Fabry registry data and assumed more plausible disutilities for infusions. However, the ERG analyses are based on assumptions that, although informed by some data, represent the ERG's best estimates. The ERG stated that limitations in the evidence remained.

4.23 The ERG did sensitivity analyses on the company's budget impact analysis and found that the calculations are most sensitive to the proportion of people who have amenable mutations, the prevalence of Fabry disease, and the proportion of people having treatment.

4.24 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the committee papers.

5 Consideration of the evidence

The evaluation committee reviewed the data available on the benefits and costs of migalastat, having considered evidence on the nature of Fabry disease and the value placed on the benefits of migalastat by people with the condition, those who represent them, and clinical experts. It also took into account the value for money that migalastat represents and the effective use of resources for specialised commissioning.

Nature of the condition

5.1 The committee understood that Fabry disease is a serious and progressive condition that causes a variety of symptoms and can greatly affect quality of life. It heard from patient experts that Fabry disease can cause significant disability and that people with the disease are likely to need a carer. The committee also understood that Fabry disease is a heterogeneous condition. The activity of the enzyme affected by Fabry disease (alpha-galactosidase A; alpha-gal A) varies depending on the mutation; some mutations lead to reduced enzyme activity and others produce a non-functional enzyme or no enzyme at all. The committee concluded that Fabry disease is a serious condition with a major effect on quality of life.

5.2 The committee discussed the current treatment of Fabry disease. It understood that enzyme replacement therapy (ERT) with agalsidase alfa or agalsidase beta has been the standard of care since 2001. The committee heard that ERT can provide important clinical benefits and gave some people dramatic health improvements, slowing progressive organ damage. The committee was aware that the dose of agalsidase beta may be reduced when the condition is stable, although the effectiveness of this unlicensed dose is not fully established and practice varies between centres. The clinical experts noted in particular that because Fabry disease is progressive, it may be difficult to define 'stability', and clinicians and people with the disease are often reluctant to risk symptoms worsening and progressive organ damage. The committee understood that ERT has a number of limitations. These include an inconvenient dosing schedule every 2 weeks causing variation in enzyme levels, risk of infusion-related reactions and infections and the possibility of developing antibodies against treatment. The

clinical experts suggested that there is also the theoretical possibility of limited penetration of ERT into key tissues. They advised that the decision about which ERT to use is usually made by the patient because there is no clear clinical difference between the 2 therapies apart from infusion time and risk of infusion-related reactions. The details of each therapy are explained to the person, who may also seek advice from family members already having treatment. People on ERT have the option of switching between the 2 therapies if needed. The committee concluded that ERT is an established treatment but there are still some unmet needs for people with Fabry disease.

5.3 The clinical experts explained that there are specific criteria for starting ERT for Fabry disease, primarily based on evidence of early clinical signs of kidney, heart or brain involvement. The committee was aware that the starting criteria for ERT for Fabry disease are described in the UK adult Fabry disease standard operating procedures (Hughes et al. 2013). Most men and roughly half of women have disease that meets these criteria when diagnosed. Of those whose disease does not meet the criteria at diagnosis, around 10% each year will progress to needing treatment. The clinical experts envisaged using the same starting criteria for migalastat. The decision about which treatment to use, migalastat or ERT, would be made by the clinician and the patient. The committee concluded that migalastat could be offered as an alternative to ERT and that no major changes to the current clinical pathway for Fabry disease would be needed.

Impact of the new technology

5.4 The committee discussed how migalastat would be used in clinical practice. It heard from the clinical experts that they would expect migalastat to be an option for people with amenable mutations whose disease meets the existing starting criteria for ERT treatment. The committee understood that the UK adults Fabry disease standard operating procedure (Hughes et al. 2013) recommends that people with classical Fabry disease start ERT at diagnosis, and people with non-classical Fabry disease start ERT when disease symptoms have an impact on quality of life or there is evidence of renal disease, cardiac disease, neurovascular disease or gastrointestinal symptoms. The clinical experts stated that similar criteria would be used to determine when patients might start migalastat and the committee considered that this approach was reasonable and

consistent with the evidence it had seen. Stopping criteria for ERT include worsening of pain, deterioration of glomerular filtration rate or proteinuria, worsening heart failure symptoms and new presentation of clinically significant neurovascular disease. The patient experts noted that people with Fabry disease were very interested in a potential new treatment, and recognised the benefits of a more convenient oral option, but would make a careful decision about which treatment would be best for them, taking into account clinical effectiveness, their experience with ERT and convenience.

5.5 The committee noted that the company presented evidence from 2 randomised clinical trials, ATTRACT and FACETS, and from 2 open-label extension studies. The company stated that migalastat was comparable in effectiveness to ERT and the clinical experts gave their opinion that migalastat was at least as good as ERT. However, the committee considered that the company's clinical effectiveness evidence had considerable weaknesses. It noted that the trials had enrolled small populations, were short in relation to disease progression, and did not collect sufficient data to formally establish the clinical equivalence of migalastat and ERT. The committee noted that the pre-specified criteria for comparability of migalastat and ERT were met, but it had some reservations about the interpretation of these. The company also presented some optimistic results for renal, cardiac and composite clinical outcomes and health-related quality of life. The clinical experts advised that people on migalastat had similar renal outcomes to those on ERT and that some cardiac outcomes appeared to improve with time spent on migalastat. People on migalastat reported that pain and gastrointestinal symptoms were manageable. The committee concluded that, despite some important uncertainties in the clinical evidence, migalastat may provide similar outcomes to ERT.

5.6 The committee considered that migalastat could offer additional benefits compared with ERT infusion because it is an oral treatment. The clinical and patient experts explained that ERT infusions every 2 weeks can have a major impact on a person's home and work life. An oral treatment would allow people with Fabry disease freedom from these frequent infusions. The committee recognised that oral treatment is more convenient than an infusion every 2 weeks. However, it acknowledged that there might be some concerns about whether people would fully adhere to treatment. In particular, it heard that adherence may be difficult in some young people and people who have had a

stroke, for example. It also heard that there is a need to fast before and after taking migalastat. The committee was reassured by the clinical and patient experts that people with Fabry disease would be very motivated to continue treatment to avoid symptoms returning, but considered that it would be important to provide support to help people adhere to the treatment regimen. The committee was further reassured that the company was taking steps to support adherence. The committee concluded that an oral treatment would allow people with Fabry disease much more freedom.

5.7 The committee heard from the clinical experts that migalastat would be discussed as an option for treatment at the same time as ERT. Improvements in LVMi suggest that migalastat might be more beneficial in people with cardiac complications, but that they would not want to restrict the treatment to a particular group. The committee concluded that migalastat would likely be offered as an option to all people for whom treatment is suitable.

5.8 Migalastat is only suitable for people with specific amenable mutations. The company advised that there was variability in the in-vitro response to migalastat according to mutation, but only mutations for which migalastat produced substantial increases in enzyme activity were judged amenable. Migalastat does not work in people who have mutations that do not produce any alpha-gal A. The committee was advised that the heterogeneity of Fabry disease would lead to some variation in results for individual people.

5.9 The committee heard that people have genetic testing when diagnosed, or when a close family member is diagnosed, as part of established practice in the NHS. The results of these tests can be checked against the migalastat amenability table. The company explained that any unknown mutations would be tested for amenability at no cost to the NHS. The committee concluded that this approach was acceptable and did not expect this testing to have any additional resource implications for the NHS. The committee understood that its recommendations would apply only to people with amenable mutations, consistent with migalastat's marketing authorisation.

5.10 Although the ATTRACT results met the pre-specified criteria for comparability between migalastat and ERT, the committee concluded that the evidence for overall clinical effectiveness of migalastat is uncertain and advised that more

long-term data are needed. The committee therefore recommended that the company, treatment centres and NHS England should collect further evidence on the effectiveness of migalastat compared with ERT, particularly on the long-term benefits of treatment.

Cost to the NHS and Personal Social Services

5.11 The committee heard details of the estimated 5-year budget impact for migalastat. It was aware that the company had proposed a patient access scheme in which migalastat would be available with a discount. It was also aware that agalsidase alfa and agalsidase beta are available in the NHS with discounts. The results of the budget impact analysis, the migalastat patient access scheme discount and the ERT discounts are confidential and cannot be reported here. The committee concluded that the budget impact analysis showed that migalastat would be associated with savings for the NHS, compared with ERT.

5.12 The committee noted that the budget impact analysis was based on the company's estimate that migalastat might be considered for 142 people in England. This estimate was based on the prevalence of Fabry disease, the proportion of people diagnosed, the proportion of diagnosed people having treatment with ERT, and the prevalence of amenable mutations. The committee recalled that the clinical experts would consider migalastat for people whose disease meets the existing starting criteria for ERT treatment (see section 5.3). The estimate was considered reasonable by the clinical experts. Although new mutations are being added to the migalastat amenability table, the experts stated that the proportion of people for whom migalastat was suitable was unlikely to change substantially. The committee concluded that the company's estimate for the number of people for whom migalastat would be considered was reasonable.

5.13 The committee accepted the estimated net budget impact for migalastat based on the current prices of migalastat, agalsidase alfa and agalsidase beta. However, it noted that the results were highly sensitive to these prices. The committee highlighted that the prices of agalsidase alfa and agalsidase beta, and therefore the net budget impact for migalastat, may change if the national tenders for these drugs were renegotiated.

Value for money

5.14 The committee noted that the company presented a cost–consequence analysis based on a Markov model. The committee considered that the company's approach and the structure of the model were generally reasonable, after discussion with the clinical and patient experts. The committee noted that the evidence review group (ERG) commented on a number of limitations in the company's model, and presented exploratory analyses to address these limitations. The main assumption in the model was clinical equivalence between migalastat and ERT. The committee recalled that the available evidence was consistent with this assumption (see sections 5.4 to 5.10) and therefore concluded that it was reasonable. However, the committee noted that the evidence was limited and uncertain, particularly for long-term outcomes.

5.15 The committee noted that the company used average weight from the general population to calculate the doses of ERT needed for treatment. This was questioned by the ERG, who commented that the average weight of people included in the clinical trials was low. However, the clinical experts considered that the average body weight of people with Fabry disease is not much different to that of the general population. The committee therefore concluded that the most appropriate body weights to use in the model were uncertain.

5.16 The committee noted that the company modelled the effect of disease complications on quality of life using disutilities. These disutilities were the same for end-stage renal disease, stroke and heart complications. The ERG had concerns about this, because they are very different conditions in terms of their effects on quality of life. The patient and clinical experts emphasised that each of these complications has a major effect on quality of life. The committee concluded that there were uncertainties about the disutilities for disease complications.

5.17 The committee noted that the infusion disutility had a substantial impact on incremental quality-adjusted life years (QALYs). The ERG stated that this disutility lacked face validity and was higher than the disutility for developing disease complications. The ERG reduced the infusion disutility by 50% in its preferred analysis. The committee recalled that patient and clinical experts stated that the oral administration of migalastat is a major advantage of this treatment, and that

changing to an oral drug from an infusion could have substantial benefits. The committee accepted that oral delivery is an improvement compared with infusion. But it questioned the size of the disutility, noting that having an infusion was unlikely to reduce health-related quality of life to the same extent as developing a new disease complication. The committee concluded that it is plausible that migalastat is associated with more health benefits than ERT as a result of its more convenient administration, but the ERG's estimates were more likely than the company's estimates. Even then, the size of the benefit is highly uncertain because of the limited evidence. The results of the company's economic model showed that migalastat is associated with an incremental QALY gain of 0.98 compared with ERT. When the infusion disutility was decreased by 50% in the ERG's preferred analysis, the incremental QALYs reduced to 0.34 compared with ERT.

5.18 The committee noted the ERG's comment that the background mortality data used in the model produced an unexpectedly high life expectancy (83.4 years) for people with Fabry disease. It also noted that the model did not allow for people developing end-stage renal disease to stop treatment with migalastat.

5.19 The committee noted that ERG scenario 6 (when migalastat is stopped because of end-stage renal disease) was inappropriate because the clinical experts advised that some of these people would resume ERT, leading to both additional costs and additional benefits. Therefore, the true impact of people stopping migalastat because of end-stage renal disease would be much smaller than suggested by this scenario analysis. The committee concluded that the company and ERG scenario analyses show a range of possibilities, the majority of which are consistent with the evidence.

5.20 The committee discussed the total and incremental costs associated with migalastat, taking into account the patient access scheme for migalastat and the discounts for ERT. These results are commercial in confidence and cannot be reported here. The committee was aware that in the company base case and the ERG preferred analysis, migalastat was associated with lower costs than ERT. The committee concluded that the overall results were highly uncertain but consistent with migalastat providing additional health benefits at a lower cost compared with ERT, but the size of any additional benefits was highly uncertain.

5.21 The committee noted that the value of migalastat has only been assessed compared with ERT, and therefore migalastat should only be recommended for people with Fabry disease for whom ERT would otherwise be offered. It considered that this was appropriate, given the scope for the evaluation and the established use of ERT in current clinical practice. However, the committee emphasised that because NICE has not evaluated ERT, the benefits and value for money of ERT have not been formally considered. It therefore considered that, by extension, the benefits and value for money of migalastat were uncertain. The committee heard from NHS England that there was evidence to suggest that ERT may not provide value for money and therefore NHS England supported the need for an evaluation of all disease-modifying treatments for Fabry disease. The committee decided that its conclusions on the value for money of migalastat were appropriate given the current evidence and clinical practice, but that they would need to be reconsidered if ERT was no longer available in routine practice. It further concluded that a complete evaluation of the costs and benefits of ERT for Fabry disease would be valuable, and requested that NHS England considers doing such an evaluation.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

5.22 The committee noted that there were a number of limitations of ERT because it is an infusion. As an oral therapy, migalastat may help to address some of these limitations and so have additional benefits beyond direct health benefits. The company presented infusion disutilities to capture this. Additional savings from the reduced need for homecare were also captured in the model.

5.23 The committee noted concerns that the once every other day dosage of migalastat could lead to low adherence, particularly for example for people with neurological problems because of stroke. The patient expert explained that symptoms of the disease return within 1 week of stopping treatment, which is likely to help adherence. For people who need extra support, the clinical experts explained that a mobile phone reminder app and other strategies can be used with the help of expert centre staff.

Conclusion

5.24 The committee acknowledged that Fabry disease is a serious condition that has severe effects on the lives of people with the condition, as well as their families and carers. It considered the evidence suggesting that migalastat has comparable effectiveness to ERT, and heard the experiences of the patient and clinical experts. It concluded that the evidence had considerable limitations but, on balance, migalastat was likely to provide similar benefits to ERT. The committee understood that migalastat may have additional benefits because it is taken orally rather than as an infusion. The committee considered that the company's economic model was broadly appropriate and that the ERG's exploratory analyses presented a range of possibilities that were consistent with the evidence. It concluded that migalastat provides the additional health benefits of an oral therapy at a lower cost compared with ERT, but that the clinical effectiveness evidence was highly uncertain. The committee accepted that, in the context of current clinical practice, the value of migalastat compared with ERT had been shown, although it noted that NICE has not evaluated ERT. The committee concluded that the case for national commissioning of migalastat is supported when used as an option for treating Fabry disease in people over 16 for whom ERT would otherwise be offered. It also concluded that further evidence on both the long-term effectiveness of migalastat and a full evaluation of the costs and benefits of ERT for Fabry disease would be valuable.

5.25 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation. It therefore concluded that the PPRS payment mechanism was not relevant in considering the value for money of the technology in this evaluation.

Summary of evaluation committee's key conclusions

Evaluation title: Migalastat for treating Fabry disease		Section
Key conclusion		
Migalastat is recommended, within its marketing authorisation, as an option for treating Fabry disease in people over 16 years of age with an amenable mutation, only if migalastat is provided with the discount agreed in the patient access scheme, and only if enzyme replacement therapy (ERT) would otherwise be offered. Criteria for starting and stopping ERT for Fabry disease are described in the UK adult Fabry disease standard operating procedures (Hughes et al. 2013). With the discount provided in the patient access scheme, migalastat has a lower total cost than ERT, and potentially provides greater health benefits than ERT.		1.1
Current practice		
Nature of the condition, including availability of other treatment options	The committee understood that Fabry disease is a progressive condition that causes a variety of symptoms and can greatly affect quality of life. It heard from patient experts that Fabry disease can cause significant disability and that people with the disease are likely to need a carer. The committee concluded that Fabry disease is a serious condition with a major effect on quality of life.	5.1
	The committee understood that ERT with agalsidase alfa or agalsidase beta has been the standard of care since 2001. The committee heard that ERT can provide important clinical benefits and gave some people dramatic health improvements, slowing progressive organ damage. The committee concluded that ERT is an established treatment but there are still some unmet needs for people with Fabry disease.	5.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee understood that ERT has a number of limitations. These include an inconvenient dosing schedule every 2 weeks causing variation in enzyme levels, risk of infusion-related reactions and infections and the possibility of developing antibodies against treatment. The clinical and patient experts explained that ERT infusions every 2 weeks can have a major impact on a person's home and work life. An oral treatment, such as migalastat would allow people with Fabry disease freedom from these frequent infusions.	5.2, 5.6
Adverse reactions	The summary of product characteristics lists adverse reactions for migalastat including: headache, gastrointestinal disorders, skin rash and itching, depression, palpitations, muscle spasms, pain, tiredness, vertigo, shortness of breath, nosebleeds, weight gain, paraesthesia, proteinuria and increased creatine phosphokinase levels. For full details of adverse reactions and contraindications, see the summary of product characteristics.	3.2
Clinical evidence		
Availability, nature and quality of evidence	The company presented evidence from 2 randomised clinical trials, ATTRACT and FACETS, and from 2 open-label extension studies. The company stated that migalastat was comparable in effectiveness to ERT and the clinical experts gave their opinion that migalastat was at least as good as ERT.	5.5
	The company presented results for renal, cardiac and composite clinical outcomes and health-related quality of life. The clinical experts advised that some cardiac outcomes appeared to improve with time spent on migalastat. People on migalastat reported that pain and gastrointestinal symptoms were manageable. The committee concluded that, despite some important uncertainties in the clinical evidence, migalastat may provide similar outcomes to ERT.	5.5

Uncertainties generated by the evidence	The committee considered that the company's clinical effectiveness evidence had considerable weaknesses. It noted that the trials had enrolled small populations, were short in relation to disease progression, and did not collect sufficient data to formally establish the clinical equivalence of migalastat and ERT.	5.5
Impact of the technology	The committee considered that migalastat could offer additional benefits compared with ERT infusion because it is an oral treatment. The committee recognised that oral treatment is more convenient than an infusion every 2 weeks. The committee was reassured that the company was taking steps to support adherence. The committee concluded that an oral treatment would allow people with Fabry disease much more freedom.	5.6
Cost evidence		
Availability and nature of evidence	The committee noted that the company presented a cost–consequence analysis based on a Markov model. The committee considered that the company's approach and the structure of the model were generally reasonable, after discussion with the clinical and patient experts. However, the committee noted that the evidence was limited and uncertain, particularly for long-term outcomes.	5.14
Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	The ERG was concerned that the effects of disease complications on quality of life were the same for end-stage renal disease, stroke and heart complications. The committee concluded that there were uncertainties about the disutilities for disease complications. The committee accepted that oral delivery is an improvement compared with infusion, but questioned the size of this benefit. The committee concluded that it is plausible that migalastat is associated with more health benefits than ERT as a result of its more convenient administration, but the size of the benefit is highly uncertain because of the limited evidence.	5.16, 5.17

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee noted that the company modelled the effect of disease complications and the effect of frequent infusions on quality of life using disutilities. It considered that there were uncertainties about the disutilities for disease complications and infusions. The committee noted that there were a number of limitations of ERT because it is an infusion, and migalastat may help to address some of these limitations and so have additional benefits beyond direct health benefits.	5.16, 5.17, 5.22
Cost to the NHS and PSS	The committee heard details of the estimated 5-year budget impact for migalastat. It was aware that the company had proposed a patient access scheme in which migalastat would be available with a discount. It was also aware that agalsidase alfa and agalsidase beta are available in the NHS with discounts. The results of the budget impact analysis, the migalastat patient access scheme discount and the ERT discounts are confidential and cannot be reported here. The committee concluded that the budget impact analysis showed that migalastat would be associated with savings for the NHS, compared with ERT.	5.11

	The committee accepted the estimated net budget impact for migalastat based on the current prices of migalastat, agalsidase alfa and agalsidase beta. However, it noted that the results were highly sensitive to these prices. The committee highlighted that the prices of agalsidase alfa and agalsidase beta, and therefore the net budget impact for migalastat, may change if the national tenders for these drugs were renegotiated.	5.13
Value for money	The committee discussed the total and incremental costs associated with migalastat, taking into account the patient access scheme for migalastat and the discounts for ERT. These results are commercial in confidence and cannot be reported here. The committee concluded that the overall results were highly uncertain but consistent with migalastat providing additional health benefits at a lower cost compared with ERT, but the size of any additional benefits was highly uncertain.	5.20
	The committee decided that its conclusions on the value for money of migalastat were appropriate given the current evidence and clinical practice, but that they would need to be reconsidered if ERT was no longer available in routine practice.	5.21
Impact beyond direct health benefits and on the delivery of the specialised service	The committee noted that there were a number of limitations of ERT because it is an infusion. As an oral therapy, migalastat may help to address some of these limitations and so have additional benefits beyond direct health benefits. The company presented infusion disutilities to capture this. Additional savings from the reduced need for homecare were also captured in the model.	5.22
Additional factors taken into account		
Access schemes	The Department of Health and the company have agreed that migalastat will be available to the NHS with a patient access scheme which makes migalastat available with a discount. The size of the discount is commercial in confidence.	6.3

Equalities considerations and social value judgements	There were no potential issues relating to equality considerations that needed to be discussed by the committee.	–

6 Implementation

6.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

6.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has Fabry disease and the doctor responsible for their care thinks that migalastat is the right treatment, it should be available for use, in line with NICE's recommendations.

6.3 The Department of Health and the company have agreed that migalastat will be available to the NHS with a patient access scheme which makes migalastat available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Alasdair MacCulloch, Regional Market Access Director at Amicus Therapeutics, amacculloch@amicusrx.com.

7 Recommendations for further research

7.1 The committee noted that there were limitations and uncertainties in the evidence presented for migalastat. It encourages the company, NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits and costs of migalastat and enzyme replacement therapy (ERT) for treating Fabry disease.

8 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser, associate director and a project manager.

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