

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Migalastat for treating Fabry disease

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using migalastat in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (the [evaluation report](#)).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of migalastat in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation determination (FED).
- Subject to any appeal by consultees, the FED may be used as the basis for NICE's guidance on using migalastat in the context of national commissioning by NHS England.

For further details, see the [Interim Process and Methods of the Highly Specialised Technologies Programme](#).

The key dates for this evaluation are:

Closing date for comments: 10 November 2016

Second evaluation committee meeting: 22 November 2016

Details of membership of the evaluation committee are given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Recommendations

- 1.1 The case for national commissioning of migalastat is supported when used within its marketing authorisation, as an option for treating Fabry disease in people over 16 with amenable mutations. With the discount agreed in the patient access scheme, migalastat provides health benefits at a lower cost than enzyme replacement therapy (ERT) at its current price.
- 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 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%.

- 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 producing alpha-gal A to which migalastat can bind are known as amenable mutations. Migalastat has a marketing authorisation in the UK for 'treating Fabry disease in people aged 16 and over with amenable mutations'. Migalastat is a lifelong treatment taken every other day.
- 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.

4 Evidence submissions

The evaluation committee (section 9) 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 to not be amenable to migalastat, according to an updated amenability assay (aligned to the marketing authorisation). 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 their own prespecified 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 m²/year or less, and the overlap in the 95% confidence intervals for these means was greater than 50%.
- 4.6 The company stated that the prespecified criteria for comparability of migalastat and ERT in ATTRACT were met for both the co-primary outcomes of measured and estimated glomerular filtration rate. The results were considered confidential and cannot be reported here. In FACETS, glomerular filtration rate was measured over 6 months, although the company stated that this is generally considered too short to show a reliable trend.
- 4.7 Patients in FACETS who continued into the open-label extension study had left ventricular mass index recorded after 18 and 24 months of migalastat. The results were considered confidential and cannot be reported here. There were no statistically significant differences in cardiac outcomes reported in the migalastat and ERT arms of ATTRACT.
- 4.8 ATTRACT included a composite clinical outcome of the rates of prespecified renal, cardiac and cerebrovascular events and mortality over 18 months. The proportion of patients who had a renal, cardiac or cerebrovascular event or who died 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 5 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 the SF-36 results for vitality and general health and stated that the other domains were stable. 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 (48-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 population is the proportion of the total number of people assumed to be having treatment for Fabry disease in the UK who would have amenable mutations for migalastat treatment (it was assumed that 40% of people with Fabry disease will have amenable mutations). 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 prespecified 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 submission. 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 lead to an overestimation of life expectancy in the model. The ERG noted that the disutility associated with ERT infusion (-0.05) was high, 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 given the differences in the methods used for calculation.

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 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 lead 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 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 GLA 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 provided some people with dramatic health improvements, slowing progressive organ damage. The committee was aware that the dose of agalsidase beta can be reduced when the condition is stable, although the effectiveness of this approach 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 may have a number of potential limitations including, limited penetration in key tissues, inconvenient administration every 2 weeks leading to variation in enzyme levels, risk of infusion-related reactions and infections, and the possibility of developing antibodies against treatment.

The clinical experts 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 infusion-related reactions. The details of each therapy are explained to the person, who may also seek advice from family members already receiving 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. 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 whose disease meets the existing starting criteria for ERT treatment. 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. However, the company presented some optimistic results for renal, cardiac and composite clinical outcomes and health-related quality of life. The committee noted that the prespecified criteria for comparability of migalastat and ERT were met, but it had some reservations about the interpretation of these. 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, but acknowledged that there might be some concerns about whether people would fully adhere to treatment (in particular, for example, some young people and people who have had a stroke). The committee was reassured by the clinical and patient experts that people with Fabry disease would be very motivated to continue treatment to avoid the return of symptoms, but considered that it would be important to provide support to help people adhere to the treatment

regimen. The committee concluded that an oral treatment would allow people with Fabry disease much more freedom.

- 5.7 The clinical experts advised that migalastat would be discussed as an option for treatment at the same time as ERT. The committee heard the experts 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. It 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, that is, mutations producing alpha-gal A to which migalastat can bind. Migalastat does not work in people who have mutations that do not produce any alpha-gal A. 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. 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. The results of these tests can be checked against the migalastat amenability table, a list compiled by the company of all known amenable mutations. 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.
- 5.10 Although ATTRACT 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, specialist 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 indicated 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 considered 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 agreed 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 the disutility lacked face validity and is 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 questioned the size of the disutility, noting that it would be unlikely that having an infusion would 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 ERG noted 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 that 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 (see section 3.3). 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. It considered that this was appropriate, given the scope for the evaluation and the established use of ERT in 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 requests that NHS England considers doing a complete evaluation of the costs and benefits of ERT for Fabry disease.

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 the effects 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 mobile phone apps 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. It accepted that 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. It also concluded that further evidence on both the short- and 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		
	The case for national commissioning of migalastat is supported when used within its marketing authorisation, as an option for treating Fabry disease in people over 16 with amenable mutations. With the discount agreed in the patient access scheme, migalastat provides health benefits at a lower cost than enzyme replacement therapy (ERT) at its current price.	1.1
Current practice		
Nature of the condition, including availability of other treatment options	The committee understood that Fabry disease is a serious condition that affects life expectancy and quality of life. 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.	2.2
	There is no cure for Fabry disease. Current treatment options are infusions with 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. Before ERT was introduced in 2001, people with Fabry disease had palliative care.	2.3
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 there are a number of potential limitations of ERT because of its administration by infusion every 2 weeks. It may also need the help of a nurse or carer for administration. Additional limitations include, limited penetration in key tissues, inconvenient administration every 2 weeks leading to variation in enzyme levels, risk of infusion-related reactions and infections, and the possibility of developing antibodies against treatment. As an oral therapy, migalastat avoids these infusion-associated issues and is expected to allow people with Fabry disease more freedom.	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 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.	4.2
	The final outcomes reported in ATTRACT and FACETS can be grouped into renal function, cardiac function, health-related quality of life and safety outcomes. The trials also reported biochemical outcomes of Gb3 and plasma lyso-Gb3 distributions and activity of the enzyme alpha-galactosidase A (alpha-gal A).	4.3
Uncertainties generated by the evidence	The company stated that migalastat was comparable in effectiveness to ERT and the clinical experts stated 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 concluded that, despite some important uncertainties in the clinical evidence, migalastat may provide similar outcomes to ERT.	5.5

Impact of the technology	The committee heard that migalastat will be an option for people with Fabry disease whose disease meets the existing starting criteria for ERT treatment. 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.	5.4
Cost evidence		
Availability and nature of evidence	The company presented a cost–consequence analysis comparing migalastat with ERT. The analysis was based on a Markov model with a lifetime time horizon and a 1-year cycle length. The analysis was done from the perspective of the NHS and Personal Social Services (PSS), and costs and benefits were discounted at a rate of 3.5% per year.	4.11, 5.14
	The company presented a budget impact analysis to predict the costs of migalastat for the NHS and PSS.	5.11
Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	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. However, it was noted that the evidence was limited and uncertain, particularly for long-term outcomes. The company modelled the effect of disease complications on quality of life using disutilities. Disutilities for the infusion administration method were also included.	5.14, 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 model captured health-related quality of life by assigning utility scores to each health state. The utility scores were taken from a Dutch study and described the health-state utility scores (disutility) for the complication states. The committee noted that the company used the same disutility for end-stage renal disease, stroke and heart complications. The committee agreed that there were uncertainties about the disutilities for disease complications. Infusion-related disutilities were based on a discrete choice experiment done by the company with 506 people from the UK general population.	4.15, 5.16

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 indicated that migalastat would be associated with savings for the NHS, compared with ERT.	5.11
	The results of the company's budget impact analysis were highly sensitive to the prices of ERT and migalastat. 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 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.	5.20
	The committee noted that the value of migalastat has only been assessed compared with ERT. It considered that this was appropriate, given the scope for the evaluation and the established use of ERT in 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 requests that NHS England considers doing a complete evaluation of the costs and benefits of ERT for Fabry disease.	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. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations.	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 [NICE to add details at time of publication]

7 Proposed 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 long-term benefits of migalastat and enzyme replacement therapy (ERT) for treating Fabry disease.
- 7.2 The committee noted that NICE has not formally evaluated ERT (agalsidase alfa and agalsidase beta) for treating Fabry disease. The committee requests that NHS England considers doing a complete evaluation of the costs and benefits of ERT for Fabry disease.

8 Proposed date for review of guidance

- 8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance, or sooner if the prices of enzyme replacement therapies (agalsidase alfa and agalsidase beta) for Fabry disease change. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

October 2016

9 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.

Kimberley Carter

Technical Analyst

Ian Watson

Technical Adviser

Leanne Wakefield and Jenna Dilkes

Project Managers

Sheela Upadhyaya

Associate Director

ISBN: To be added by editor before publication