National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Migalastat for treating Fabry disease

Response to consultee and commentator comments on the draft remit, draft scope and provisional matrix

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Amicus Therapeutics	Yes. Migalastat represents an innovative and alternative therapeutic option to current enzyme replacement therapy. Migalastat is an oral medication with equivalent efficacy to current intravenous therapy in genetically amenable Fabry patients. As such it will result in a change in service provision.	Comment noted.
	Genetic Alliance UK	Although the NHS in England routinely commissions enzyme replacement therapy (ERT) for patients with Fabry disease, ERT has limitations such as insufficient biodistribution of recombinant enzymes and high costs. Migalastat has a novel method of action, being pharmacological chaperone therapy, and as yet no medicine of this type has been evaluated for use in England (an HST evaluation of eliglustat for Gaucher disease was initiated but has been suspended since November 2014). We consider that the HST appraisal route (limited to three evaluations per year) should be reserved for novel products that do not match accepted paradigms of treatment, and migalastat falls into this category.	Comment noted.
	MPS Society	Appropriate	Comment noted.
	Royal College of Pathologists	Yes - there are key questions to be addressed regarding the utility & cost effectiveness of this treatment	Comment noted.
	Royal Free London NHS Foundation Trust	Yes	Comment noted.
Wording	Amicus	Yes we agree with the current wording.	Comment noted.

Section	Consultees	Comments	Action
	Therapeutics		
	Genetic Alliance UK	Yes	Comment noted.
	Royal College of Pathologists	It may be helpful to clarify that migalastat may only be appropriate for treating a subset of patients with Fabry disease i.e. those with responsive mutations.	Comment noted. The remit is intentionally broad to allow consideration of all patients with Fabry disease should the marketing authorisation be broader than the trial population. The population of the draft scope currently reflects the clinical trial population, namely people with Fabry disease with a confirmed GLA mutation that is amenable to migalastat in vitro.
	Royal Free London NHS Foundation Trust	yes	Comment noted.
Timing Issues	Amicus Therapeutics	Marketing authorisation approval is expected in early 2016. Given that genetically amenable patients can then be offered a straightforward transition to oral therapy from current Intravenous ERT this will expand patient therapy options. In addition, this will result in a change in terms of service provision and expediency of review may allow sufficient time for NHS England planning	Comment noted.
	Genetic Alliance UK	Migalastat does not yet have marketing authorisation in Europe, though the application was accepted for accelerated evaluation in July 2015. Thus the timing of this proposed HST evaluation is appropriate.	Comment noted.

Section	Consultees	Comments	Action
	MPS Society	Important although we recognised that there are already two other treatments approved and in use for Fabry disease.	Comment noted.
	NHS England	Migalastat is an alternative to existing therapy so there is perhaps not the urgency associated with the launch of a new therapy for previously untreatable disease. Urgency will also depend on how the product is priced - if priced substantially lower than the existing therapies the proposed evaluation becomes more urgent.	Comment noted.
	Royal Free London NHS Foundation Trust	-This is a novel therapy bring oral treatment to patients with Fabry disease. There have been substantial issues in relation to home care provision for patients receiving enzyme replacement therapy with difficulties with deliveries and storage resulting in significant impact on QOL for Fabry patients. For migalastat homecare could consist of a simple postal delivery removing the necessity for costly home care and difficulties with infusions.	Comment noted.

Comment 2: the draft scope

Background information	Amicus Therapeutics	The background information is broadly correct, although the number of patients in UK is underestimated, with approximately 450 identified patients currently on ERT.	Comment noted. The scope has been updated to reflect this.
	Genetic Alliance UK	The estimate of 120 people in England with Fabry disease we understand to be calculated based on the prevalence suggested in the quoted NIHR HTA. However, we understand that the MPS Society has some 370 Fabry patients registered in the UK, and estimates actual incidence to be nearer to 450 in the UK, which indicates the number of people in England with Fabry disease to be closer to 380.	Comment noted. The scope has been updated to reflect this.
	Genzyme Therapeutics (a	Whilst it is stated on page 1, paragraph 4, sentence 2 that it is estimated that there are about 150 people with Fabry Disease in	Comment noted. The scope has been updated to reflect this.

	Sanofi company).	England, we note that there are about 500 people treated for this disease in the UK.	
	MPS Society	The number of UK patients diagnosed with Fabry disease in our opinion exceeds the 120 stated. We would estimate this number to be nearer to 400-450. Reported outcomes, indicates that pain is still an area of burden for many adult sufferers.	Comment noted. The scope has been updated to reflect this.
	Royal College of Pathologists	The information appears incomplete as it does not reference a) the large number (>450) mutations in the GLA gene b) the potential problems in assessing pathogenicity. The results of in silico analysis may be unclear and functional studies are generally not readily available or that robust. c) complexity of genotype–phenotype correlation in Fabry disease	Comment noted. The scope has been updated to reflect the incidence of Fabry disease in England. The background section is intended as a brief summary of background information. The details regarding the problems in assessing pathogenicity complexity of genotype-phenotype correlation will be considered during the evaluation.

	Royal Free London NHS Foundation Trust	Other body sites that can also be affected include the skin, eyes, kidneys, heart, brain and nervous system'- it should be emphasized that these effects are QoL and survival limiting. Both male and female patients suffer from cardiomyopathy with cardiomyopathy, heart failure, arrhythmias requirement for pacemaker, cardiac transplantation, renal failure with dialysis or transplantation, stroke. These are not rare occurrences and will results in the early death of male and female patients with both classical and later onset Fabry disease •'some alpha-galactosidase A activity, in which case symptoms develop between the ages of 60 and 80 years'- presentation of later onset disease is usually in the 5th of sixth decade for index cases but earlier for patients diagnosed as a result of family screening . Males in their 40s often already have cardiac hypertrophy and benefit from therapy before the onset of cardiac fibrosis and arrhythmias. It has been estimated that there are approximately 120 people in England with Fabry disease- ' this is an underestimate as there are over 300 in my clinic alone	Comment noted. The scope has been updated to reflect the cardiac and renal involvement due to Fabry disease, as well as the increased risk of stroke.
The technology/ intervention	Amicus Therapeutics	Yes it is accurate	Comment noted.
	Genetic Alliance UK	It appears likely based on the currently ongoing clinical trials that Amicus will seek a marketing authorisation for migalastat both as a monotherapy for patients with the amenable mutation, and as a treatment in combination with existing ERT, however the draft scope does not reflect this.	Comment noted.
	Genzyme Therapeutics (a Sanofi company).	Under the section titled "Technology / Intervention" on page 2, paragraph 2, sentence 2, we believe, should read as below with an additional third and fourth sentence added: It has been studied as monotherapy in clinical trials in people aged 16 years or older with Fabry disease who have a mutation in the GLA gene that is known to be responsive to migalastat in vitro, compared with placebo although the means by which patients who	Comment noted. The background section is intended as a brief summary of background information. The issues raised in your comment will be considered during the evaluation.

		may respond to the treatment will be identified in clinical practice has yet to be confirmed. It is estimated that about 30-40% of patients have this mutation and that treatment will probably be restricted to those with higher residual enzyme activity and consequently milder disease. In considering the dosing of the comparators in the clinical trial programme of migalastat care should be taken in determining whether these equate to the recommended doses of agalsidase alfa and beta as stipulated in their respective SPCs	
	MPS Society	Appropriate	Comment noted.
	Royal College of Pathologists	It is unclear how and to what extent it will be feasible to determine and classify whether a mutation is responsive to migalastat? Mutations may have variable penetrance. How will this issue be addressed. Will it impact on access?	Comment noted. The issue raised in your comment will be considered during the evaluation.
	Royal Free London NHS Foundation Trust	GLA gene that is known to be responsive to migalastat in vitro, compared with placebo' comparators in the phase 3 clinic trials include current therapy ie enzyme replacement	Comment noted.
Population	Amicus Therapeutics	Yes – only patients who demonstrate a mutation, which is either directly measured or historically shown to be responsive to migalastat therapy should be considered.	Comment noted.
	MPS Society	Appropriate	Comment noted.
	NHS England	This is an X linked disease. Females are affected but cost effectiveness may differ between males and females.	Comment noted.
	Royal College of Pathologists	The population is not adequately defined. For pragmatic reasons it may be necessary to limit the assessment to more common mutations which might also introduce some inequality.	Comment noted. The company has identified approximately 800 migalastat-amenable mutations. These are catalogued and when a person's GLA gene is sequenced at screening/diagnosis. Once the sequence of the gene is known, it can

			be checked against the company's database. If the mutation does not currently exist in the database, the company will, at its own cost, assay the mutation in vitro to test for amenability. According to the company, the threshold of the assay for amenability is fixed and will not change over time
	Royal Free London NHS Foundation Trust	People with Fabry disease with a confirmed GLA mutation that has been shown to be responsive to migalastat in vitro- you might wish to use the term' amenable' rather than responsive to avoid confusion between in vitro activity and clinical response and to be in line with the accepted terminology in the community	Comment noted. The population has been updated to reflect your suggestion.
Comparators	Amicus Therapeutics	Agalsidase alpha and beta are appropriate comparators used at their licensed doses.	Comment noted.
	Genetic Alliance UK	Yes	Comment noted.
	MPS Society	Reported outcomes indicate that Migalastat is comparable to Agalsidase alpha and Agalsidase beta.	Comment noted.
	NHS England	The comparators are correctly identified as agalsidase alfa and beta. There is however an issue about what dose regime to use for the comparison, particularly for agalsidase beta.	Comment noted.
	Royal Free London NHS Foundation Trust	Yes- it is not possible to clinically distinguish these two products so both should be considered	Comment noted.
Outcomes	Amicus Therapeutics	All outcome measures are appropriate, but we would suggest adding other measurable parameters of cardiac disease, such as LVMi (Left ventricular mass index). Since the majority of Fabry patients will succumb to cardiac disease, it remains the singularly	Comment noted. Measurable parameters of cardiac disease have now been included in the scope.

		most important symptom group that should be considered. Homecare, nurse support and home delivery will all be impacted by the introduction of oral administration and cost effectiveness measures relating to these should be specifically considered.	The scope only specifies health outcomes that will be considered during the evaluation. It is anticipated that the cost of homecare, nurse support and home delivery will be incorporated into the company's economic modelling of migalastat for treating Fabry disease.
	Genetic Alliance UK	We understand that clinical trials suggest that migalastat has a level of effectiveness similar to existing enzyme replacement therapies, and so one of the primary benefits of migalastat over existing ERT is that it can be taken orally rather than by blood infusion. This has the potential to improve quality of life for patients and their carers, and the outcome measures in the draft scope should reflect this. Additionally, oral therapy at home rather than blood transfusions at a specialist clinical centre would likely result in significant savings to the NHS on costs of administering treatments, and so the evaluation must consider this impact.	Comment noted. The scope only specifies health outcomes that will be considered during the evaluation. It is anticipated that the cost of homecare, nurse support and home delivery will be incorporated into the company's economic modelling of migalastat for treating Fabry disease.
	Genzyme Therapeutics (a Sanofi company).	We would suggest that an additional outcome should be plasma lyso-GL	Comment noted. Plasma lyso-Gb3 has been included in the scope.
	MPS Society	Appropriate	Comment noted.
	Royal Free London NHS Foundation Trust	• Gb3 levels in kidney and urine- this is not very helpful for assessment of clinical response. Lyso GB3 is the appropriate measures • cardiac function - include architecture	Comment noted. Plasma lyso-Gb3 and cardiac function been included in the scope. Gb3 levels in the urine have been removed from the scope.
Equality	MPS Society	Appropriate	Comment noted.
	Royal College of Pathologists	There may be rare variants for which it will either be extremely demanding to assess likely responsive status and this may well correlate with minority ethnicities.	Comment noted. Although a variant may be rare, once it is sequenced, it can be tested by the company for amenability to migalastat. The

			company will, at its own cost, assay the mutation in vitro to test for amenability. According to the company, the threshold of the assay for amenability is fixed and will not change over time. According to clinical experts attending the scoping workshop, there is no link between race and Fabry disease.
Other considerations	Amicus Therapeutics	The introduction of a self-administered oral medication into a patient group where IV infusions have been the mainstay of therapy for 15 years will have significant impact on service needs and potential costs associated. We believe that special consideration should be given to assessing the impact of release of capacity/funding that this change of therapy can offer.	Comment noted.
	Genetic Alliance UK	We understand from the patient support group that there is a level of nervousness amongst Fabry disease patients, who might be reluctant to switch to migalastat from ERT for fear that, if it is ineffective, they will be unable to switch back. The evaluation must therefore consider treatment continuation rules.	Comment noted.
	Royal College of Pathologists	Over 450 different mutations have been described in the GLA gene, ~60% of which are missense (and therefore potentially migalastat-responsive), but only a small proportion have been fully assessed for their responsiveness to migalastat/molecular chaperones. Therefore, would treatment be initiated for: a) only mutations that are some 'approved list' as being assessed as responsive b) What is the process (technical & financial) for determining and curating this list? c) what is the status of partially responsive mutations?	Comment noted. The company has identified approximately 800 migalastat-amenable mutations. These are catalogued and when a person's GLA gene is sequenced at screening/diagnosis. Once the sequence of the gene is known, it can be checked against the company's database. If the mutation does not currently exist in the database, the company will, at its own cost, assay the mutation in vitro to test for amenability. According to the company, the threshold of the assay

			for amenability is fixed and will not change over time.
Innovation	Amicus Therapeutics	Yes, this first in class pharmacological chaperone represents a change in administration and thus patient choice, homecare services, infusion services and patient convenience.	Comment noted.
	Genetic Alliance UK	Yes	Comment noted.
	MPS Society	The benefit of taking a tablet every other day may be preferable to patients having to undergo an IV infusion every two weeks or weekly in some instances. The drug has only been trialled in adults, so at present not appropriate for children.	Comment noted.
	NHS England	Migalastat is a chaperone therapy not enzyme replacement and hence innovative in its mode of action. The innovative benefit to patients arises because it is given orally not intravenously.	Comment noted.
	Royal Free London NHS Foundation Trust	This is new modality of therapy which is oral and will impact for that reason on quality of life however improved tissue penetration and lack of generation of antibodies which occur with the iv product is likely to impact positively on efficacy	Comment noted.
Questions for consultation	Amicus Therapeutics	*Will people with either standard or atypical presentations of Fabry disease be suitable for treatment with migalastat?* Patients considered appropriate for treatment by their clinician and whose disease is secondary to recognised amenable mutations are suitable for migalastat therapy. There are no other clinical considerations necessary. These patients will have already been identified under existing clinical guidelines *What proportion of people with Fabry disease is expected to have a GLA mutation that has been shown to be*	Comments noted.

		responsive to migalastat? Estimations are that between 40 and 50% of currently treated Fabry patients would express one of the 800 mutations currently identified that are genetically amenable to migalastat therapy. *What proportion of people is undiagnosed or experiences a late diagnosis?* Patients suitable for migalastat therapy will be already diagnosed with Fabry disease. The presenting symptoms and age at presentation are very heterogeneous. It is not expected that any significant change in diagnostic pattern will occur as a result of the introduction of migalastat therapy. *How many people are likely to switch from their current ERT to migalastat?* Approximately 40-50% of currently diagnosed patients will have genetically amenable mutations and will thus respond to migalastat therapy. The expectation is that many patients will find an oral medication preferable to an intravenous infusion, however some may stay on IV ERT for personal or clinical rationale. *Have all relevant comparators for migalastat been included in the scope?* Yes	
	Genetic Alliance UK	We understand that it is estimated that 60% of patients with Fabry disease have the mutation which makes them suitable for migalastat treatment as monotherapy.	Comment noted.

	MPS Society	It is our understanding that approximately 60% of Fabry patients, may have a GLA mutation. It is anticipated that there may be a level of nervousness from patients in switching therapies, due to the uncertainty within NHS England. Patients may be reluctant to switch in case migalastat does not prove to be effective and they cannot switch back to ERT. Consideration needs to be given to this. Patients may prefer to take a tablet every other day rather than have bi-weekly infusions. Cost savings may be made, due to there not being a need for homecare. As patients would be self-administering, consideration should be given to the development of a compliance strategy. Given the potential cost of the drug, how will the drug be prescribed and what would the means of delivery be?	Comment noted.
	Royal Free London NHS Foundation Trust	• Will people with either standard or atypical presentations of Fabry disease be suitable for treatment with migalastat? - Suitability for migalastat will depend on the amenability of the mutation. Data from phase three studies shows that this range of patients includes both those with early classical and later onset disease (I would avoid using the terminology of standard and atypical as the meaning is unclear and Fabry is very heterogeneous so most patient are atypical in some way). • What proportion of people with Fabry disease is expected to have a GLA mutation that has been shown to be responsive to migalastat? Approx. 60% • What proportion of people is undiagnosed or experiences a late diagnosis? - Approx. 20% patient have 'late diagnosis', others are diagnosed promptly on presentation of symptoms and others are diagnosed early due to cascade screening within families	Comment noted.

		• How many people are likely to switch from their current ERT to migalastat? -on the basis that 60% might be eligible and half of these may switch I would estimate approx. 30% current patients Have all relevant comparators for migalastat been included in the scope? Yes • Which treatments are considered to be established practice for treating Fabry disease in England? Fabrazyme and Replagal in addition to palliative and supportive therapies Are there any subgroups of people in whom migalastat is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately? - other than the amenability criteria I am not aware of any subgroup effect Please describe any existing services in England for the diagnosis, management and treatment of Fabry disease. NHSE highly specialised recognised centres for the diagnosis and management of lSDs and specialised laboratories • Will additional diagnostic infrastructure be required to identify people with a GLA mutation that is responsive to migalastat? - No -the manufacturer has a look up table and has assessed amenability of new mutations that periodically present	
Additional comments on the draft scope	Royal College of Pathologists	There are a number of NHS provider laboratories that undertake both enzymatic and sequence analysis for Fabry disease. Some of this falls within the current scope of highly specialised commissioning for lysosomal storage disorders. Information is needed as to whether these providers could/should also provide the required functional studies alongside sequence analysis, in silico prediction and X-inactivation (& phases assessment).	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Royal College of Nursing

Comment 3: the provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	All LSD specialist centres should be added	Amicus		Noted	All LSD specialist centres have been included in the Final Matrix
2.	Remove Guy's & St Thomas' NHS Foundation Trust	NICE Secretariat		Removed	This organisation's interests are not directly related to the evaluation topic and as per our inclusion criteria Guy's & St Thomas' NHS Foundation Trust has not been included in the matrix of consultees and commentators.