NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technology Evaluation

Migalastat for treating Fabry disease

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of migalastat within its licensed indication for treating Fabry disease for national commissioning by NHS England.

Background

Fabry disease (also known as Anderson-Fabry disease) is an inherited lysosomal storage disorder caused by mutations in the GLA gene which encodes the enzyme alpha-galactosidase A. Mutations in the GLA gene change the enzyme's structure and function and prevent it from breaking down a fat called globotriaosylceramide (Gb3). Progressive accumulation of Gb3 in cells can lead to a wide range of symptoms which may not appear in everyone with the disease.[1]

The number and severity of symptoms varies between patients and can include short term severe pain or burning sensation, which starts at the extremities and spreads throughout the rest of the body (often referred to as a 'Fabry crisis'), gastrointestinal complications such as diarrhoea, nausea and abdominal pain, headaches, inability to sweat properly (hypohidrosis), vertigo and hearing impairment. Other body sites that can also be affected include the skin, eyes, kidneys, heart, brain and nervous system. Symptoms usually worsen as patients get older, except pain, which often improves after childhood.[2]

Fabry disease is X-linked, therefore men who have only one copy of the defective gene are more likely to develop the disease.[3] Men can have either:

- no alpha-galactosidase A activity, in which case symptoms will usually develop during childhood and be quite severe (this is the standard presentation); or
- some alpha-galactosidase A activity, in which case symptoms develop between the ages of 60 and 80 years (this is atypical and these men can remain asymptomatic for many years before being diagnosed with Fabry disease).[3]

Because women have two X chromosomes, enzyme activity is extremely variable due to random X-chromosomal activation. Therefore, some women will have no disease activity, while others may have mild, moderate or severe symptoms. It has been estimated that there are approximately 120 people in England with Fabry disease.[3]

There is currently no cure for Fabry disease. Enzyme replacement therapy (agalsidase alfa and agalsidase beta) are administered to replace the non-functioning enzyme[2] and help prevent the development of disease-related symptoms in younger patients, and slow disease progression in people with more advanced disease.[4] For people with severe kidney disease, a kidney

transplant may be considered. Fabry disease and related conditions (collectively termed lysosomal storage diseases) are usually managed in specialist centres in England.

The technology

Migalastat (Galafold, Amicus Therapeutics) is a molecule that binds with and refolds the faulty alpha-galactosidase A enzyme to restore its activity. This allows it to enter the lysosome and to break down Gb3. It is administered orally.

Migalastat does not currently have a marketing authorisation in the UK. 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. Migalastat has been studied in people who have not received previous treatment, and in those who have previously received enzyme replacement therapy.

Intervention(s)	Migalastat
Population(s)	People with Fabry disease with a confirmed GLA mutation that has been shown to be responsive to migalastat in vitro
Comparators	• Agalsidase alpha • Agalsidase beta
Outcomes	The outcome measures to be considered include: • symptoms of Fabry disease (including pain) • Gb3 levels in kidney and urine • kidney function • cardiac function • progression-free survival (time to occurrence of renal, cardiac, neurological and cerebrovascular events) • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options

Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Cost to the NHS and Personal Social Services (PSS), and Value for Money	• budget impact in the NHS and PSS, including patient access agreements (if applicable) • robustness of costing and budget impact information • technical efficiency (the incremental benefit of the new technology compared to current treatment) • productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • staffing and infrastructure requirements, including training and planning for expertise.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation.Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If appropriate, the evaluation should include consideration of the costs and implications of additional testing for genetic mutations, but will not make recommendations on specific diagnostic tests.
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. http://www.england.nhs.uk/wpcontent/uploads/2013/06/e06-lyso-stor-dis-child.pdf NHS England Standard Contract for Metabolic Disorders (Adult), 2013. http://www.england.nhs.uk/wpcontent/uploads/2013/06/e06-metab-disordersadult.pdf Department of Health rare diseases strategy, November 2013. https://www.gov.uk/government/publications/rare-diseases-strategy

Questions for consultation

- Will people with either standard or atypical presentations of Fabry disease be suitable for treatment with migalastat?
- What proportion of people with Fabry disease is expected to have a GLA mutation that has been shown to be responsive to migalastat?
- What proportion of people is undiagnosed or experiences a late diagnosis?
- How many people are likely to switch from their current ERT to migalastat?

Have all relevant comparators for migalastat been included in the scope?

- Which treatments are considered to be established practice for treating Fabry disease in England?

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?

Please describe any existing services in England for the diagnosis, management and treatment of Fabry disease.

- Will additional diagnostic infrastructure be required to identify people with a GLA mutation that is responsive to migalastat?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which migalastat will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access migalastat;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: http://www.nice.org.uk/media/DE4/9A/HSTCombinedInterimProcessMethods.pdf.

References

1. O'Mahoney C, Elliot P (2010) Anderson-Fabry disease and the heart. Progress in Cardiovascular Diseases 52(4):326-35

2. MPS Society (2013) Guide to Understanding Fabry Disease.

3. Connock M, Juarez-Garcia A, Frew E et al. (2006) A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1. NIHR Health Technology Assessment programme: Executive Summaries 10(20).

4. Lidove O, West M, Pintos-Morrell G et al. (2010) Effects of enzyme replacement therapy in Fabry disease—A comprehensive review of the medical literature. Genetics in Medicine 12, 668–679.

5. Desnick R, Brady R, Barranger J et al. (2003) Fabry Disease, an Under-Recognized Multisystemic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy. Annals of Internal Medicine 138:338-346.