Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Pegunigalsidase alfa for treating Fabry disease

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of pegunigalsidase alfa within its marketing authorisation for treating Fabry disease.

Background

Fabry disease (also known as Anderson–Fabry disease) is an X-linked inherited lysosomal storage disorder. It is caused by mutations in the GLA gene, which encodes the enzyme alpha-galactosidase A (α-Gal A). Mutations in the GLA gene cause the enzyme to be lacking or have reduced activity, preventing it from breaking down a fat called globotriaosylceramide (Gb3). Gb3 then progressively accumulates in cells and tissues, causing progressive damage to multiple organs.[1]

The onset, number and severity of symptoms varies substantially between patients, and can depend on the amount of remaining α-Gal A enzyme activity. 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.

Symptoms 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. Fabry disease can lead to potentially life-threatening complications such as heart and renal failure and an increased risk of stroke.[2]

The estimated prevalence of Fabry disease is 1 in 49,000 people, meaning there are approximately 1,150 people with Fabry disease in England. [3,4]

There is no cure for Fabry disease. Current treatment options include infusions with enzyme replacement therapies, agalsidase alfa and agalsidase beta, which replace the non-functioning enzyme. Some patients have the option to receive these infusions within their own home, administered by visiting healthcare professionals.[5] These treatments relieve the symptoms of Fabry disease and prevent progression of damage to organs such as the kidney and the heart.[2] NICE highly specialised technology 4 (HST 4) recommends migalastat for people over 16 with Fabry disease with amenable mutations. For people with severe kidney disease, a kidney transplant may be considered. Adjunctive therapies include treatment of pain, hypertension and cutaneous lesion of capillaries known as angiokeratoma.

Appendix B

The technology

Pegunigalsidase alfa (PRX-102, Chiesi), is a novel enzyme replacement therapy for the treatment of Fabry disease. It is produced in a plant cell-based system, in contrast to the existing therapies which are produced in hamster or human cell lines.[6] It is administered via intravenous infusion and delivers a modified version of α-Gal A, which is lacking in people with Fabry disease. The enzyme is chemically modified in a way that makes it more stable than current enzyme replacement therapies, potentially extending the time between treatments.[7] Similar to existing enzyme replacement therapies, the treatment can be administered in the patient's home by healthcare professionals.[8]

Pegunigalsidase alfa does not currently have a marketing authorisation in the UK. It has been compared with existing enzyme replacement therapies in clinical trials. The trial participants were adults aged 18 years or older who had been diagnosed with Fabry disease and had previously received an enzyme replacement therapy.

Intervention(s)	Pegunigalsidase alfa
Population(s)	People with Fabry disease
Comparators	• Agalsidase alpha • Agalsidase beta • Best supportive care • Migalastat (*for those aged over 16 years with an amenable mutation*)
Outcomes	The outcome measures to be considered include: • symptoms of Fabry disease (including pain) • Gb3 levels in kidney • plasma lyso-Gb3 levels • kidney function • cardiac function and disease measurements (such as left ventricular mass index) • event-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).

Appendix B

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
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.
Related NICE recommendations	Related Highly Specialised Technologies guidance: 'Migalastat for treating Fabry disease' (2017). NICE Highly specialised technologies guidance 4. Review date February 2020. Migalastat for treating Fabry disease (nice.org.uk) Related NICE Pathways: Endocrine, nutritional and metabolic conditions overview NICE pathway Endocrine, nutritional and metabolic conditions overview - NICE Pathways
Related National Policy	NHS England (2018) Highly specialised services 2018 Lysosomal storage disorders service (children & adults) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf NHS England Standard Contract for Metabolic Disorders (Adult), 2013. https://www.england.nhs.uk/wp-content/uploads/2013/06/e06-metab-disorders-adult.pdf Department of Health rare diseases strategy, November 2013. https://www.gov.uk/government/publications/rare-diseases-strategy The NHS Long Term Plan, 2019. https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/

Appendix B

	NHS England. NHS manual for prescribed specialist services (2018/2019). Chapter 71. Lysosomal storage disorder service (adults and children). https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/

Questions for consultation

Is the population defined appropriately?

- How many people are living with Fabry disease in the UK? Among them, how many are aged 18 years and above?
- Would patients currently having enzyme replacement therapy be eligible for pegunigalsidase alfa?
- Would patients currently having migalastat be eligible for pegunigalsidase alfa?
- Are there people with Fabry disease who are not currently having enzyme replacement therapy or migalastat for whom pegunigalsidase alfa could be considered?

One of the company's pivotal trials assessed the treatment effect of pegunigalsidase alfa in patients who had taken enzyme replacement therapy in comparison with continued use of enzyme replacement therapy:

- Would pegunigalsidase alfa be used after other enzyme replacement therapies, or as an alternative to enzyme replacement therapies in clinical practice?
- For people with Fabry disease and amenable mutations, would pegunigalsidase alfa be used after migalastat, or as an alternative to migalastat in clinical practice?
- Where do you consider pegunigalsidase alfa will fit into the existing 'Endocrine, nutritional and metabolic conditions overview' NICE pathway'?

Have all relevant comparators for pegunigalsidase alfa included in the scope? How should best supportive care be defined?

Which treatments are considered to be established clinical practice in the NHS for Fabry disease?

Are the outcomes listed appropriate?

What important benefits have the other enzyme replacement therapies currently in routine use (agalsidase alfa or agalsidase beta) and migalastat provided to people with the condition?

Appendix B

What additional benefits pegunigalsidase alfa would provide to people with the condition (for example, in terms of frequency of administration, acceptability among people with Fabry disease and so on)?

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

In addition to agalsidase alfa, agalsidase beta, and migalastat, are there other treatments that are available or will become available for treating Fabry disease?

Would pegunigalsidase alfa be a candidate for managed access?

Do you consider pegunigalsidase alfa 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)?

Do you consider that the use of pegunigalsidase alfa can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

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 pegunigalsidase alfa 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 the technology;

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

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. Is there any reason to evaluate this as a Multiple Technology Appraisal Process? (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

Appendix B

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. https://www.mpssociety.org.uk/fabry-disease Accessed 2nd Feb 2022

3 Brennan, P. and Parkes, O. (2014) Case-finding in Fabry disease: experience from the North of England. Journal of inherited metabolic disease, 37 (1): 103–107

4 Office for National Statistics, 2020 mid-year estimate for England population

5 Royal Free London NHS Foundation Trust. Lysosomal storage disorders - Treatment and services. Available at https://www.royalfree.nhs.uk/services/services-a-z/lysosomal-storage-disorders/treatment-and-services/ Accessed 22nd Feb 22.

6 Azevedo, O., et al. (2021). Fabry disease therapy: state-of-the-art and current challenges. International Journal of Molecular Sciences, 22(1), 206.

7 Schiffmann, R., et al. (2019). Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: a 1-year phase 1/2 clinical trial. Journal of inherited metabolic disease, 42(3), 534-544.

8 Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of BRIDGE Phase III Open-Label, Switch-Over Clinical Trial Evaluating Pegunigalsidase Alfa for the Treatment of Fabry Disease (2020). Available at https://protalixbiotherapeutics.gcs-web.com/news-releases/news-release-details/protalix-biotherapeutics-and-chiesi-global-rare-diseases-2. Accessed 22nd Feb 22.