Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Pegunigalsidase alfa for treating Fabry disease

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of pegunigalsidase alfa within its marketing authorisation for treating adults with 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 symptomatic Fabry disease is 1 in 49,000 people, meaning there are approximately 1,150 people with symptomatic Fabry disease in England. [3,4] When including people with asymptomatic or presymptomatic Fabry, the prevalence is expected to be higher.[5]

There is no cure for Fabry disease but treatments are available which relieve the symptoms and prevent progression of damage to organs such as the kidney and the heart.[2] In the UK, people typically start taking Fabry-specific medicines when the starting criteria outlined in the BIMDG treatment guidelines are met.[6] 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.[7] For people over 16 with amenable mutations, NICE highly specialised technology 4 (HST 4) recommends migalastat as an alternative treatment option to enzyme replacement therapy. Migalastat is taken orally (by mouth) and it works by binding to the alpha-galactosidase A enzyme as it is made, improving its function. 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.

The technology

Pegunigalsidase alfa (PRX-102, Chiesi), is a novel enzyme replacement therapy for the treatment of adults with Fabry disease. It would be offered to those people who would usually be offered ERT or migalastat. It is produced in a plant cell-based system, in contrast to the existing therapies which are produced in hamster or human cell lines.[8] 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.[9] Similar to existing enzyme replacement therapies, the treatment can be administered in the patient's home by healthcare professionals.[10]

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)	Adults with Fabry disease
Subgroups	• People who have an amenable mutation and are on migalastat
Comparators	• Agalsidase alpha • Agalsidase beta • Migalastat (*for those aged over 16 years with an amenable mutation*)

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Outcomes	The outcome measures to be considered include: • symptoms of Fabry disease (including pain and gastrointestinal issues such as diarrhoea, nausea and abdominal 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).
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 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

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	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 and Social Care UK Rare Disease Framework, January 2021 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950651/the-UK-rare-diseases-framework.pdf The NHS Long Term Plan, 2019. https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/ 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/

References

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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 Gragnaniello, V., et al. (2021). Newborn Screening for Fabry Disease in Northeastern Italy:

6 Hiwot T, Hughes D, Ramaswami U. BIMDG: Guidelines for the treatment of Fabry Disease 2020 www.bimdg.org.uk/store/lsd//FabryGuide_LSDSS_Jan2020_700523_11032020.pdf. Accessed May 2022

7 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.

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

9 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.

10 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.