NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Lenadogene nolparvovec for treating Leber's hereditary optic neuropathy caused by the G11778A ND4 mitochondrial mutation

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of lenadogene nolparvovec within its marketing authorisation for treating Leber's hereditary optic neuropathy caused by the G11778A ND4 mitochondrial mutation.

Background

Leber's hereditary optic neuropathy (LHON) is an inherited genetic condition, which causes rapid loss in vision. It is caused by alterations in the DNA of the mitochondria (structures in the cells responsible for metabolising carbohydrates and fatty acids into energy that the cells can use). These mutations increase the oxidative stress experienced by retinal ganglion cells leading to cell damage and cell death. Retinal ganglion cells communicate visual information to the brain through fibres forming the optic nerve. When these cells are dead, they are unable to send signals to the brain causing vision loss and blindness. The loss of vision is painless and initially occurs in 1 eye, with the other eye usually affected within 2 to 3 months.[1,2] The degree of vision loss varies but typically is severe enough to be registered as severely sight impaired. In some people, additional extraocular (non-vision related) symptoms may develop. This is referred to as 'LHON plus' and can include symptoms similar to multiple sclerosis, such as muscle weakness, poor coordination, and numbness.

The onset of the symptoms of LHON most commonly occurs in a person's late teens through to their early thirties, though vision loss can also appear in early childhood or late adulthood. LHON disproportionately affects males, as 50% of male carriers, but only 10% of female carriers, will develop the disease.[3] It is estimated that 1 in 25,000 people in the UK are affected.[4] Around 50% to 75% of people with LHON will have the G11778A ND4 mitochondrial mutation.[5-7]

There are currently few treatment options for LHON, and significant improvements in vision are rare. There is currently no NICE guidance for LHON. Idebenone has a marketing authorisation in the UK for LHON. However, it is not currently commissioned for routine use in the NHS in England. Clinical management in England focuses on monitoring, psychological support and visual rehabilitation (for example, teaching people how to use aids for low vision), neuro-ophthalmologist visits and social care support.

The technology

Lenadogene nolparvovec does not currently have a marketing authorisation in the UK for LHON. It has been studied in clinical trials, compared with placebo and sham, in people with LHON caused by the G11778A ND4 mitochondrial mutation.

Intervention(s)	Lenadogene nolparvovec
Population(s)	People with Leber's hereditary optic neuropathy caused by the G11778A ND4 mitochondrial mutation
Subgroups	If the evidence allows the following subgroups will be considered. These include: • those with recent vision loss
Comparators	Established clinical management including: • visual aids • occupational/low vision rehabilitation • lifestyle management Idebenone (subject to NICE topic selection and evaluation)
Outcomes	The outcome measures to be considered include: • visual acuity • contrast sensitivity • retinal nerve fibre layer/macular thickness • immune response • visual field assessment • adverse effects of treatment • health-related quality of life.

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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The use of lenadogene nolparvovec is conditional on the presence of the G11778A ND4 mutation. The economic modelling should include the costs associated with diagnostic testing for G11778A in people with Leber's hereditary optic neuropathy who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation). Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.
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 Quality Standards:** 'Serious eye disorders' (2019). NICE quality standard 180. **Related Evidence Summaries**: 'Mitochondrial disorders in children: Co enzyme Q10' (2017) NICE Evidence summary 11.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) NHS England (2019). Clinical Commissioning Policy: Idebenone for treating people over 12 years of age with Leber's Hereditary Optic Neuropathy

References

1 Yu-Wai-Man P, Turnbull DM, Chinnery PF. Leber hereditary optic neuropathy. J Med Genet 2002;39:162–169

2 Harding AE, Sweeney MG, Govan GG, Riordan-Eva P. Pedigree analysis in Leber hereditary optic neuropathy families with a pathogenic mtDNA mutation. Am J Hum Genet 1995;57:77-86.

3 Brown MD, Wallace DC. Spectrum of mitochondrial-DNA mutations in Lebers hereditary optic neuropathy. Clin Neurosci 1994;2:138-45

4 Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT, Taylor RW, Bindoff LA, Turnbull DM. The epidemiology of pathogenic mitochondrial DNA mutations. Ann Neurol 2000;48:188-93

5 LHON Society. About LHON. Accessed September 2022.

6 Yu-Wai-Man P, Griffiths PG, Brown DT, Howell N, Turnbull DM, Chinnery PF. The Epidemiology of Leber Hereditary Optic Neuropathy in the North East of England. Am J Hum Genet 2003;72:333-339

7 Meyerson C, Van Stavern G, McClelland C. Leber hereditary optic neuropathy: current perspectives. Clin Ophthalmol. 2015;9:1165-1176.