

Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Draft scope

Draft remit/appraisal 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 70% 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 is the only treatment that has a marketing authorisation in the EU for LHON. However, NHS England has published a [Clinical Commissioning Policy](#) that concludes that there is insufficient evidence to support a policy for the routine commissioning of idebenone. 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 (Lumevoq, GenSight Biologics) is a gene therapy that uses an adeno-associated virus vector to deliver the wild-type (non-mutated) ND4 gene directly to the mitochondrial membrane of the retinal ganglion cells. ND4 is one of the most commonly mutated genes associated with LHON. When mutated, it disrupts the process of converting oxygen, fats, and simple sugars to energy. This leads to the

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death of cells in the optic nerve and the specific symptoms of LHON. Lenadogene nolparvovec is administered via intravitreal injection.

Lenadogene nolparvovec does not currently have a marketing authorisation in the UK for LHON. It has been studied in clinical trials, compared with placebo, 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
Comparators	Established clinical management including visual aids, occupational/low vision rehabilitation and lifestyle management
Outcomes	The outcome measures to be considered include: <ul style="list-style-type: none">• visual acuity• contrast sensitivity• retinal nerve fibre layer/macular thickness• immune response• visual field assessment• visual evoked potentials• adverse effects of treatment• health-related quality of life.

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<p>Economic analysis</p>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>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.</p> <p>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. <u>See section 5.9 of the Guide to the Methods of Technology Appraisals</u>.</p> <p>Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.</p>
<p>Other considerations</p>	<p>If the evidence allows the following subgroups will be considered. These include those with recent vision loss.</p> <p>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.</p>
<p>Related NICE recommendations and NICE Pathways</p>	<p>Related Quality Standards:</p> <p>'Serious eye disorders' (2019). NICE quality standard 180.</p> <p>Related Evidence Summaries:</p> <p>'Mitochondrial disorders in children: Co enzyme Q10' (2017) NICE Evidence summary 11.</p> <p>Related NICE pathway:</p> <p>'Eye conditions overview' (2020).</p>
<p>Related National Policy</p>	<p>The NHS Long Term Plan, 2019. NHS Long Term Plan</p> <p>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019)</p> <p>Department of Health and Social Care, NHS Outcomes</p>

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	Framework 2016-2017: Domains 2, 4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017
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Questions for consultation

Have all relevant comparators for lenadogene nolparvovec been included in the scope? Which treatments are considered to be established clinical practice in the NHS for LHON? Is idebenone used in routine clinical practice for LHON?

Are the outcomes listed appropriate? Should outcomes related to the non-vision related symptoms of LHON be included?

Are there any subgroups of people in whom lenadogene nolparvovec is expected to be more clinically effective and cost effective or other groups that should be examined separately?

What percentage of people with LHON present with the G11778A ND4 mutation? To what extent are people with LHON currently tested for the G11778A ND4 mutation in clinical practice in the NHS?

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 lenadogene nolparvovec 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.

Do you consider lenadogene nolparvovec 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 lenadogene nolparvovec can result in any potential significant and 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 Appraisal Committee to take account of these benefits.

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To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>).

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 June 2021.
- 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.