NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Lenadogene nolparvovec for treating Leber's hereditary optic neuropathy

Draft scope (pre-referral)

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.

Background

Leber's hereditary optic neuropathy (LHON) is a genetic condition inherited from the mother, 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 vision signals to the brain causing vision loss and blindness. The loss of visually is painless and initially occurs in one eye, with the other eye usually affected within two to three months.[1,2] The degree of visual loss varies but typically is severe enough to be registered as severely sight impaired.

People who carry the specific mutations of the mitochondrial DNA may or may not develop the disease. Those who will develop it will remain asymptomatic until they experience blurring or clouding of vision. The onset of symptoms most commonly occurring in a person's late teens through to 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]

There are currently few treatment options for LHON, and significant improvements in vision are rare. There is currently no guidance for LHON. Idebenone is a treatment that is marketed in the EU for LHON. Clinical management in the UK 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 (brand name unknown, GenSight Biologics) is a gene therapy that uses an adeno-associated virus (AAV) 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 results in decreased ATP synthesis, increased oxidative stress, and ultimately blindness. 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 a clinical trials, compared with placebo, in adults with LHON caused by the G11778A ND4 mitochondrial mutation.

Intervention(s)	Lenadogene nolparvovec
Population(s)	People with Leber's hereditary optic neuropathy
Comparators	• Established clinical management including visual aids, occupational/low vision rehabilitation and lifestyle management • Idebenone
Outcomes	The outcome measures to be considered include: • visual acuity • contrast sensitivity • retinal nerve fiber layer/macular thickness • immune response • 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. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.

Other considerations	If the evidence allows the following subgroups will be considered. These include those with recent vision loss and the specific point mutation associated with the LHON diagnosis. 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 and NICE Pathways	None.
Related National Policy	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. chapter 12 (adult specialist ophthalmology services) https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 2, 4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

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 Leber's hereditary optic neuropathy?
How should 'established clinical management' be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other 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?

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.

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. P Y W Man, D M Turnbull, P F Chinnery. 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