

**Clinical
Commissioning
Policy:
Idebenone for treating
people over 12 years
of age with Leber's
Hereditary Optic
Neuropathy**

NHS England Reference: 200401P



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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between people in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About Leber's Hereditary Optic Neuropathy

Leber's hereditary optic neuropathy (LHON) is a rare inherited disease which causes sudden problems with vision. It is caused by mutations (changes) in the mitochondria (the part of cells that creates the energy needed for them to function), damaging the cells in the retina of the eye and often progressing to blindness – an average of 50% of males and 15% of females carrying a LHON mutation will lose vision in their lifetime. A LHON genetic mutation is passed on from generation to generation, and both parents can carry the mutation, however only females can pass it on to their children. Vision problems may start with a painless blurring of central vision in 1 or both eyes but around 97% of people with LHON symptoms will have both eyes affected within 1 year of diagnosis. For most people vision loss is permanent, though for some patients with certain mutations, there may be a minor degree of visual recovery without treatment. The disease can occur at any age and for both males and females, although mostly occurs in males aged 15-35 years.

About current treatments

There are no treatments currently available to treat LHON, therefore patients are only able to access supportive care. This is likely to broadly consist of (a) low vision aids, (b) registration as visually impaired, (c) genetic counselling (including reproductive options) and (d) follow-up visits, but the details may vary from centre to centre and from patient to patient.

About the new treatment

In patients with LHON, the mitochondria do not produce sufficient energy for the retina to work effectively. Idebenone is thought to help support the mitochondria and allow the retina to function more effectively. This may improve vision or prevent blindness.

What we have decided

NHS England has carefully reviewed the evidence prepared by NICE to treat visual impairment in people with LHON. We have concluded that there is not enough evidence to consider making the treatment available.

2 Introduction

Leber's hereditary optic neuropathy (LHON) is a rare maternally-inherited genetic disease which causes visual impairment. Mitochondria are responsible for converting energy locked in foodstuffs into energy that the cell can use in the form of Adenosine Triphosphate (ATP), the energy currency of the cell. Mitochondria contain their own small circular DNA (mtDNA) molecules and mutations in this mtDNA can severely disrupt the energy conversion process and produce excessive amounts of reactive oxygen species (ROS) which are damaging to proteins within the cell. Some mtDNA mutations cause this damage specifically in the retinal ganglion cells of the eye, resulting in an optic neuropathy with severe loss of central vision that was first described by Dr Theodore Leber. LHON usually starts with a painless blurring of central vision in 1 or both eyes, usually followed by progression to blindness in both eyes. Progression can be very rapid (over a period of months) or may take longer to progress (over a number of years) but around 97% of people with LHON will have both eyes affected within 1 year of diagnosis (Meyerson, 2015). Both males and females can be carriers, although only females can pass on the genetic mutation to their children. Onset can occur at any age and for both males and females, although it mostly occurs in males aged 15-35 years (Fraser, 2010). Only a proportion of those that carry the mutation will be affected; estimates vary but approximately 50% of male carriers and 20% of female carriers will be affected. Environmental influences, particularly smoking, play an important part in disease expression.

Current treatment for people with LHON is limited to best supportive care (BSC). This includes regular neuro-ophthalmology outpatient appointments, referral to low-vision services, lifestyle advice and/or genetic counselling. Sudden blindness and lack of treatments can cause severe psychological impacts for patients with LHON.

Idebenone is a short chain benzoquinone which acts on mitochondria. It is thought that idebenone will activate viable-but-inactive retinal ganglion cells, which can enable recovery of vision in people who have experienced vision loss, and help prevent people from becoming blind.

Idebenone is licensed to treat visual impairment in adolescent and adult patients with LHON.

3 Definitions

Leber's Hereditary Optic Neuropathy (LHON): a hereditary condition causing visual impairment.

Mitochondrial DNA (mtDNA): the DNA located in mitochondria.

Best supportive care (BSC): care that focuses on relieving symptoms caused by a medical condition without actively treating it.

Clinically relevant recovery (CRR): a measure that identifies clinically meaningful improvements in visual acuity.

Clinically relevant worsening (CRW): a measure that identifies clinically meaningful decline of visual acuity.

Clinically relevant stabilisation (CRS): a measure that identifies clinically meaningful maintenance of visual acuity.

Logarithm of the minimal angle of resolution (logMAR): a logarithmic scale for assessing visual acuity.

Early treatment diabetic retinopathy study (ETDRS): a chart used for standardising visual acuity testing.

Visual acuity (VA) is the measure of the ability of the eye to see fine detail.

Adverse event (AE) an unintended medical occurrence in a treatment group or individual receiving a treatment.

European public assessment report (EPAR): a set of documents describing the evaluation of a medicine authorised via the centralised procedure and including the product information, published on the European Medicines Agency website.

4 Aims and Objectives

This policy considered:

- The evidence for clinical effectiveness and safety of idebenone as a first line therapy for treating adolescents and adults with LHON.

The objectives were to:

- Define the evidence base upon which the commissioning criteria and arrangements for idebenone are established
- Define the clinical commissioning criteria and commissioning arrangements for idebenone.

5 Epidemiology and Needs Assessment

The prevalence of LHON in England has been estimated to be 3.22 to 4.4 per 100,000. This is based on 2 studies in North-East England (Man et al. 2003 and Gorman et al. 2015). Applying this to England 2018 population estimates for people aged 12 and over (47,871,600), this equates to a prevalence of **2,072** people with LHON in England.

6 Evidence Base

NHS England has concluded that there is insufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

Summary of evidence

Evidence was considered from 5 studies on the clinical effectiveness and safety of idebenone in adolescents and adults with LHON:

- One phase II randomised controlled trial (RCT) (the RHODOS trial, Klopstock et al. 2011)
- A post-hoc sub-analysis of a small population completing the RHODOS trial, focusing on colour sensitivity (Rudolph et al. 2013)
- A single time-point, open-label follow-up study of people completing the RHODOS trial (RHODOS-OFU, but reported in the EPAR only)
- A natural history case record survey of 383 cases of people with LHON (reported in the EPAR only)
- An expanded access programme (EAP), which reported on patients' clinical experience of using idebenone on a longer term-basis. Data from the original cut-off period (prior to the EMA marketing application) was reported in the EPAR).

The best evidence came from RHODOS (Klopstock et al. 2011), a 24-week double-blind, phase II RCT in people with LHON receiving either the licensed dose of idebenone, or placebo.

Visual acuity

Visual acuity (VA) was a commonly used outcome across studies, and it was measured in several different ways. Please see definitions section for a definition of the various measures of VA. VA was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, and expressed using logarithm of the minimal angle of resolution (logMAR) values. LogMAR quantifies a large range of visual abilities from 0.0 (normal vision) to 1.68 (unable to read any letter on the chart, and able to read only 1 large letter correctly at 1 metre distance). The ETDRS chart has 5 letters on 1 line, each letter is equivalent to 0.02 log units. To calculate an overall VA score, the logMAR value of the best line a person is able to read is converted by multiplying by the number of letters the person is able to read. Where change from baseline scores were reported in the studies, a positive logMAR value (showing an increasing logMAR) indicated worsening and a negative logMAR value (showing a decreasing logMAR) indicated improvement.

The primary outcome in RHODOS (Klopstock et al. 2011) was the logMAR between baseline and 24 week end-point for best recovery/least worsening of VA. This improved for people receiving both idebenone and placebo. Idebenone had a mean logMAR improvement of -0.135 (95% confidence intervals (CI) -0.216 to -0.054), equivalent to an improvement of 6 letters on the ETDRS chart, and placebo had a logMAR improvement of -0.071 (95% CI -0.176 to 0.034), equating to an improvement of 3 letters on the ETDRS chart. The estimated mean difference between groups was not statistically significant (logMAR = -0.064, 95% CI: -0.184 to 0.055); equating to a 3-letter change, $p = 0.291$).

RHODOS also measured the change from baseline to 24 weeks in best VA, VA of best eye and VA of either eye. Only VA in both eyes demonstrated statistical significance, showing an improvement for idebenone (change in logMAR -0.054; 95% CI= -0.114 to 0.005) compared with placebo (logMAR 0.046; 95% CI: -0.032

to 0.123; estimated difference between groups = logMAR -0.100; 95% CI: -0.188 to -0.012; p = 0.026).

Klopstock et al. (2011) carried out a sub-analysis of people in RHODOS with discordant VA at baseline (that is, people whose visual acuity between their eyes was different at baseline, with a difference of logMAR >0.2 between eyes). Statistically significant improvements in visual acuity for idebenone compared with placebo were found from baseline to 24 weeks for all of the 4 primary and secondary outcomes:

- Change in best recovery of visual acuity (logMAR = -0.285; 95% CI: -0.502 to -0.068; p = 0.01)
- Change in best visual acuity (difference between groups: logMAR = -0.421; 95% CI: -0.692 to -0.150; p = 0.003)
- Change in visual acuity of the patient's best eye (difference between groups: logMAR = -0.415; 95% CI: -0.686 to -0.144; p = 0.003)
- Change in visual acuity for all eyes (difference between treatment groups: (logMAR = -0.348; 95% CI: -0.519 to -0.176; p = 0.0001).

However, there were no statistically significant differences in any outcomes among people with concordant visual acuity.

The EPAR reported on a further analysis of data based on the modified ITT (mITT) population in RHODOS. The mITT population was the same as the ITT population (which had been used in the previous reported efficacy analysis) but for VA data excluded 1 person who had been randomised to placebo and was considered as a natural history confounder due to an on-going spontaneous recovery of vision at the time of randomisation into the study. The difference between treatment groups for all people remained non-statistically significant for the primary outcome, however, change in best VA at 24 weeks showed a statistically significant difference between groups in favour of idebenone (logMAR = -0.160 (95% CI = -0.289 to -0.031), 8 letters difference, p=0.015).

To define a clinically meaningful measure of improving VA RHODOS (reported in the EPAR) considered the proportion of people who achieved a clinically relevant recovery (CRR) from baseline. This was people who were able to read at least 1

row (5 letters) at 24 weeks (for people who were originally “off chart” at baseline) or 2 rows (10 letters) at 24 weeks (for people who were originally “on chart” at baseline). 16 out of 53 (30.2%) patients in the idebenone group and 2 out of 28 (7.1%) patients in the placebo group showed CRR from baseline ($p=0.0234$). By effect size, patients in the idebenone group achieved an 11 letter change (-0.23 logMAR) in total, compared with 18 letter change (-0.37 logMAR) in total in the placebo group. Furthermore, 21 eyes (19.8%) of the idebenone group achieved a CRR at 24 weeks, compared with 2 eyes (3.6%) in placebo. The difference between groups in proportion of eyes with a CRR from baseline was statistically significant in favour of idebenone ($p=0.0041$). There was no statistically significant difference in the proportion of people with a clinically relevant worsening (CRW) in best VA (from ≤ 1.6 logMAR to ‘off chart’ or a change in logMAR of 0.2 ‘on-chart’) which was recorded in 2 people (3.8%) in idebenone group and 2 people (7.1%) placebo ($p=0.6508$). The difference between treatment groups in time since disease onset to achieving a CRR was also reported as statistically significant in favour of the idebenone group (median to CRR = 42.4 months) compared with placebo (median time to CRR not reached), $p = 0.0133$.

Table 9 in the EPAR presents a comparison of the proportions of idebenone and placebo-controlled patients in the mITT population who recovered from their VA nadir (see below). A statistically significant difference in favour of idebenone was seen for patients presenting with recovery ($p=0.0321$). Statistical significance was also reached in patients with a disease duration ≥ 1 year, but there was no significant between-treatment difference for disease duration < 1 year.

Table 1 : Proportion of people with CRR from nadir at 24 weeks (mITT population)

	Idebenone n=53	Placebo n=28	p-value
Recovered from nadir (all patients)	18 of 53 (34.0%)	3 of 28 (10.7%)	P=0.0321
Recovered from nadir (duration of LHON <1 year)	5 of 19 (26.3%)	1 of 9 (11.1%)	P=0.6296
Recovered from nadir (duration of LHON ≥ 1 year)	13 of 34 (38.2%)	2 of 19 (10.5%)	P=0.0545

The VA scores in 60 of the 85 people originally in RHODOS were followed up in a single observational visit (RHODOS-OFU) at an average duration of 30 months after RHODOS had ended. Results found no statistical differences between treatment groups from RHODOS baseline to week-24, or week-24 of RHODOS to the OFU.

Further supportive evidence on the longitudinal effects of idebenone in people with LHON came from a multi-centre open-label- uncontrolled study (EAP). At the clinical cut-off date (March 2015), the EPAR reported the mean treatment duration at time of cut-off was 15.4 (range 2.8 to 36.2) months, and at that time, 34 out of 69 people (49.3%) and 55 out of 138 eyes (39.9%) experienced a CRR from VA from their lowest reported point to their last assessment.

The EPAR provided further evidence regarding the natural course of vision loss and recovery in people with LHON. Using historically documented VA data from existing medical records in a case record survey of 383 case records. These results supported the earlier findings of RHODOS and the EAP, in both the proportion of people receiving idebenone and achieving a CRR and proportion of people receiving idebenone whose VA did not decline to a CRW.

Colour contrast sensitivity

A sub-population of the RHODOS trial (39 participants at 1 centre) were assessed for colour-contrast sensitivity. Red–green (protan) and blue–yellow (tritan) colour confusion was identified using computer graphics. There was a statistically significant improvement in the tritan colour contrast in the idebenone group at 12 weeks (difference between groups: -14.51%; 95% CI: -24.19 to -4.83; $p = 0.004$) and 24 weeks (difference between groups: -13.63%; 95% CI: -23.61 to -3.66; $p = 0.008$), whereas the changes in protan colour contrast between baseline and 24 weeks did not reach statistical significance [Difference between groups = -3.9% (Cis not reported; $p=0.239$)].

Rudolph et al. (2013) further considered the changes in colour-contrast sensitivity in a post-hoc analysis and found variable results. People with discordant VA taking placebo showed a statistically significantly larger decline in both protan colour contrast sensitivity when compared with idebenone (estimated mean difference between idebenone and placebo = -16.6% $p=0.022$ at 12 weeks and -13.5% $p=0.067$ at 24 weeks) and in tritan colour contrast sensitivity (estimated mean difference = -12.7% $p=0.060$ at 12 weeks and -20.4% $p=0.005$ at 24 weeks).

In people younger than 30 years a statistically significant difference in tritan colour contrast was found in favour of idebenone compared with placebo (estimated difference between idebenone and placebo groups = -19.2%, $p=0.005$ at 12 weeks and -17. %, $p=0.010$ at 24 weeks), but the results were not statistically significant for protan colour contrast at either 12 or 24 weeks. Results for people aged 30 years or older were more inconsistent. Protan colour contrast only showed statistically significant differences between groups at 12 weeks follow-up (-15.3%, $p=0.032$), but differences in tritan colour contrast were not statistically significant at either 12 or 24 weeks.

Quality of life

Health-related quality of life was assessed in RHODOS and the RHODOS-OFU and only reported in the EPAR. The Visual Function (VF)-14 tool was used to obtain these outcomes.

The overall difference between treatment groups in change of VF-14 score at 24 weeks follow-up was not statistically significant. Similar findings were reported in the RHODOS-OFU. The overall changes between VF-14 score recorded during RHODOS and RHODOS-OFU were small and differences between idebenone and placebo groups were not statistically significant.

Health-related quality of life was also reported using the Clinician's Global Impression of Change (CGIC) score during RHODOS. The CGIC is a 3-item observer-rated scale that measures global improvement or change in illness experience. The change from baseline in CGIC scores was determined at 24 weeks, although statistical analysis was not reported. The EPAR noted that the changes at 24-week end-point were similar for people receiving idebenone and people receiving placebo.

Safety

Klopstock et al. (2011) reported that the nature, severity and frequency of the observed adverse events (AEs) in RHODOS were indistinguishable between the treatment groups. Two serious AEs were reported although both were not considered to be due to the treatment received.

The EPAR noted that the majority of AEs were mild or moderate in intensity and reported that no deaths occurred in the RHODOS study.

Similar results were found in the EAP.

Interpretation of findings

Results suggest that, although RHODOS showed idebenone improved VA, this was not statistically significant compared with placebo for the primary outcome, and follow-up results (RHODOS-OFU) showed no difference in groups in VA of best eye from either baseline or endpoint of RHODOS to time of OFU visit. The

results from sub-analyses suggest there may be some beneficial effect of idebenone in stabilising or improving VA in subgroups, particularly for people with discordant VA and the proportion of eyes achieving a clinically relevant recovery (CRR), based on the mITT analysis, was statistically significant in favour of people receiving idebenone.

Visual acuity is a measure of visual function, but it does not define the full experience of vision. The EPAR stated the primary outcome (best recovery/ least worsening) would not necessarily reflect changes in VA relevant to overall ability to see, although it did recognise that a CRR was a valuable marker for assessing treatment benefit. When vision is poor, marginal improvements of VA in some may have a substantive change in their ability to see or function.

Results of colour contrast changes suggest idebenone may be effective in improving or preserving colour vision especially in subgroups of people with discordant VA or people younger than 30 years.

There was no health-related quality of life benefit shown using either tool.

The safety analysis suggest idebenone was well-tolerated and safe at both 24 weeks follow-up and over a longer-term period.

Results should be considered with caution. RHODOS was a phase II design of a relatively small population of people at various stages of disease progression and a short follow-up. It therefore provides limited evidence on the long-term benefits of idebenone therapy. The EPAR stated “there was a risk of over-estimating the effect of idebenone because of potential for spontaneous recovery in LHON” and the reliance on the mITT analysis could lead to “uncertainties in the robustness of the RHODOS data” because the exclusion of the patient deemed a confounder resulted in considerable increase of the between-group differences.

7 Criteria for Commissioning

Not applicable.

8 Patient Pathway

Not applicable.

10 Governance Arrangements

Not applicable.

11 Mechanism for Funding

Not applicable.

12 Audit Requirements

Not applicable.

13 Documents That Have Informed This Policy

The documents that have informed this policy include a review of the clinical evidence available for idebenone. Additional evidence sources are listed in the table of references below.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is or is not for routine commissioning.

15 References

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