NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using idebenone in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: April 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using idebenone in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 16 May 2024
- Second evaluation committee meeting: 04 June 2023
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Idebenone is not recommended, within its marketing authorisation, for treating visual impairment in Leber's hereditary optic neuropathy (LHON) in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with idebenone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people, this decision should be made jointly by them, their clinician, and their parents or carers.

Why the committee made these recommendations

Standard care for LHON includes nutritional supplements, genetic counselling and lifestyle management advice. There are no licensed medicines for the underlying causes of LHON, so there is an unmet need for new treatments.

Evidence from a clinical trial directly comparing idebenone with standard care suggests that idebenone is no better at improving vision. But this is uncertain because the trial only included a small number of people and was short. Longer-term trials show that idebenone improves vision but, in these trials, it was not compared with standard care. An indirect treatment comparison also suggests that idebenone is no better than standard care at improving vision in the long term. Overall, it is uncertain how effective idebenone is compared with standard care, and further research is needed to estimate its potential benefits.

These clinical uncertainties are also present in the economic model. So, it is not clear what the most likely cost-effectiveness estimates are for idebenone. Further economic modelling is needed, and idebenone is not recommended.

2 Information about Idebenone

Marketing authorisation indication

2.1 Idebenone (Raxone, Chiesi) is indicated for the 'treatment of visual impairment in adolescent and adult patients with Leber's hereditary optic neuropathy (LHON)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the idebenone.

Price

2.3 The list price for a 180 tablets pack of 150 mg idebenone is £6,364 (excluding VAT; BNF online, accessed April 2024).

2.4 The company has a commercial arrangement, which would have applied if idebenone had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Chiesi, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical management

The condition

3.1 Leber's hereditary optic neuropathy (LHON) is caused by mutations in the genes encoding mitochondrial DNA (mtDNA). Mutations in mtDNA disrupt the synthesis of adenosine triphosphate (ATP) and produce free radicals. This damages retinal ganglion cells and destroys the optic nerve. LHON is normally inherited, if a mother carries the mutation, it may be transmitted to children. The 3 most common mutations are 11778G>A, 14484T>C and 3460G>A. These mutations are found in around 95% of the LHON population. LHON typically leads to progressive vision loss, particularly in

young adults, and mainly affects boys and men. The patient experts explained that the experience of living with LHON varies from person to person. They explained that, for them, LHON:

- came on rapidly
- is painless
- is subacute
- has caused severe loss of visual acuity (VA) and colour vision, and loss of central but not peripheral vision.

They explained that, even though peripheral vision is usually preserved initially, it may also deteriorate over time. This can lead to being registered as blind. Blurring and clouding of vision are usually the first symptoms of LHON and start in 1 eye, with the second eye following a similar progression within 4 to 6 months. The clinical experts explained that LHON is usually irreversible, but that spontaneous improvement may occur in a few people with certain LHON mutations such as 14484T>C and 3460G>A. The clinical experts noted the lack of understanding of the cause and natural history of LHON. Its course is split into subacute, dynamic and chronic phases. But this naming convention has limited significance because each phase may present differently for different people. There is what is described as a nadir, or lowest point, of VA, after which no further deterioration in central vision is expected. This may be different for each person with LHON. The committee noted the frequent rapidity of progression of LHON and the uncertainty around the mechanism of disease activity.

Unmet need

3.2 There are no licensed treatments for LHON available on the NHS in England. The clinical and patient experts explained that the rapid vision loss and deteriorating nature of the condition have a considerable effect on people's:

- independence

- education
- ability to work and occupational choices
- social life
- ability to carry out day-to-day tasks.

The patient experts explained that the condition significantly affects the lives of people with LHON because it leads to a sudden and severe loss of central vision in 1 eye then, shortly afterwards, in the other eye. In most people, chronic visual impairment remains. The sudden change in sight can make daily activities such as reading, driving and recognising faces very difficult. The patient and clinical experts explained that many people must adapt to their vision capabilities. This can include relying on assistive technologies, such as screen readers, magnifiers or speech to text software to access digital information. Also, people with LHON can feel emotional and psychological effects, including grief, frustration, anxiety and depression, and coping with vision loss also affects their families and carers. The effects can lead to an inability to work and socialise, a negative effect on education, missed career opportunities and difficulties in having relationships. The clinical experts explained that carers are often the family members of people with LHON, specifically mothers who may feel guilt for passing on the condition. The committee understood that there are no treatment options and people with LHON often have difficulty doing daily tasks. It also understood that the condition can have an impact on education and career opportunities, cause financial burdens for people and their families, and result in difficulties in having relationships. The committee concluded that LHON is a rare, serious and debilitating condition that severely affects the lives of people with it, and their families and carers.

Existing treatment

3.3 The patient and clinical experts explained that no treatment addresses the underlying cause of LHON. They explained that the current treatment option for people with LHON is limited to best supportive care. This

includes neuro-ophthalmology outpatient appointments, referral to low-vision services, lifestyle advice and genetic counselling. They explained that genetic counselling can help people with LHON and their carers understand the condition, risk factors and its inheritance. Supportive therapies such as low-vision aids and infrared light therapy may be used to help people to adjust to changes in vision and maintain independence. Lifestyle modifications are often recommended for people with LHON. These can include avoiding certain things that could potentially worsen their condition, such as tobacco, alcohol and exposure to drugs and toxins with mitochondrial toxicity. Ubiquinone (coenzyme Q10) and other substances can be used to improve mitochondrial function, reduce oxidative stress and provide alternative ATP energy sources. The clinical experts clarified that ubiquinone may be effective in other mitochondrial conditions. But they noted that the evidence suggests it is not very effective in treating LHON because it does not pass the blood-brain barrier to get to the optic nerve. The committee noted that managing LHON is complex and individualised, and that there is no effective treatment for LHON. It concluded that standard care is the appropriate comparator and would be given in addition to idebenone.

Clinical-effectiveness evidence

Data sources for idebenone

3.4 For the clinical effectiveness and safety of idebenone in people with LHON, evidence from 4 studies was considered. These were:

- RHODOS: a double-blind randomised placebo-controlled trial assessing the efficacy and safety of idebenone in 85 people over 24 weeks of treatment. It included people aged 14 to 64 years with impaired VA in at least 1 eye because of LHON with an onset of visual loss of 5 years or less, and a confirmed diagnosis (m.11778G>A, m.14484T>C or m.3460G>A LHON mtDNA mutations identified).

- RHODOS observational follow up (OFU): a single-visit observational follow-up study of 58 people with LHON assessing the long-term efficacy of idebenone. It included people in the RHODOS trial in either the idebenone or placebo arms, but who were not expected to have idebenone after RHODOS finished. Median follow up was 30 months (range: 20.9 to 42.5 months).
- LEROS: an open-label intervention study assessing the efficacy and safety of long-term treatment with idebenone in 199 people 12 years and over with LHON. It lasted 24 months, with visits taking place at months 1, 3, 6, 9, 12, 18 and 24.
- Expanded access program (EAP): a real-world-evidence open-label multicentre retrospective analysis of long-term treatment with idebenone in 111 people with LHON with an onset less than 5 years from baseline. It included people 12 years and over with an onset of vision loss of less than 12 months before starting idebenone.

The committee noted that the main evidence came from RHODOS. RHODOS-OFU was the long-term follow-up for people previously randomised to idebenone or placebo in RHODOS. LEROS and EAP provided data on the long-term effectiveness of idebenone for LHON. The committee noted that RHODOS was a high-quality randomised controlled trial, but had a small sample size and provided limited evidence on the long-term effects of idebenone. RHODOS-OFU provided data that was based on a single visit 30 months after RHODOS finished. The people included did not have idebenone between the end of RHODOS and their follow-up visit. The EAP provide long-term data on people with LHON who had idebenone on an individual basis for 36 months. The committee noted that, when the RHODOS study was started, there was a lack of detailed natural history studies on LHON. Also, the optimum length of time needed to detect the impact of treatment was not known. So, further non-randomised studies such as the EAP and LEROS were included in the idebenone development program.

Comparator data (CaRS natural history studies)

3.5 The company used data from the case record survey (CaRS) natural history studies to inform the comparative effectiveness of the standard-care comparator. This was because of the lack of long-term randomised data in the EAP, RHODOS-OFU and LEROS. The CaRS studies were retrospective non-interventional studies of existing medical records of people with a genetically confirmed diagnosis of LHON. The EAG explained that the CaRS studies had a large proportion of missing data, and a high degree of variability in the availability of data from people with LHON at different time points. The committee noted that the lack of long-term comparator data meant that the company used an indirect treatment comparison (ITC) to compare idebenone with standard care. The committee noted that the CaRS studies were international studies with CaRS 1 reporting natural history data for 383 people with LHON and CaRS 2 reporting natural history data for 219 people with LHON. The committee noted that the CaRS studies did not provide direct comparative evidence on long-term treatment with idebenone compared with standard care. It also noted that there was a lot of missing data and a high degree of variability in the availability of data from different people at different time points. The committee concluded that using data from the CaRS studies was acceptable to inform comparative effectiveness in the context of this evaluation. But it considered that further characterisation of natural history using the data could be attempted, rather than only using a limited number of data points.

Outcomes

3.6 The company trial measured outcomes such as VA, clinically relevant recovery, contrast sensitivity, visual field assessment and adverse effects. It provided analyses for many outcomes at the level of an individual eye (for example, change in the logarithm of the minimal angle of resolution [LogMAR] VA of individual eyes) and at the level of the patient (for example, change in the LogMAR VA of a patient's best eye). It based its

economic model on VA based on the LogMAR VA transitions seen in the clinical evidence. The company noted the difficulty in collecting outcome data on VA and relating it to quality of life for LHON. This was because both eyes may be affected at different time points, so each person's VA at baseline was not always clear. The EAG considered the change in a person's best eye would most closely be linked to quality of life. The patient experts explained that, during their visual field assessment, they noted that their peripheral vision improved over time to compensate for losses in central vision. They thought this might explain minor improvements in VA without idebenone. The committee was aware that common outcomes used to evaluate best VA and colour sensitivity were presented as secondary outcomes. The committee agreed that the best VA was broadly acceptable as an outcome to inform the assessment of efficacy of idebenone. But it noted potential limitations of the sensitivity of the outcome if describing smaller treatment effects.

Results

3.7 In RHODOS, the primary outcome was best recovery of VA for people with improving VA in either eye or least worsening of VA for people whose VA was not improving in either eye, between baseline and week 24. This was identified using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and expressed using LogMAR values. The primary outcome improved both for people having idebenone and people having placebo. With idebenone, there was a mean LogMAR improvement of -0.135 (95% confidence intervals [CI] -0.216 to -0.054). This equated to an improvement of 6 on the ETDRS chart. With placebo, there was a LogMAR improvement of -0.071 (95% CI -0.176 to 0.034). This equated 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; p=0.291). This equated to a 3 letter change. In the RHODOS intent-to-treat (ITT) population, for the change in best VA in the best eye at week 24 compared with the best VA in the best eye at baseline, the difference between idebenone and standard care did

not reach statistical significance. In people having idebenone, the LogMAR slightly improved (change -0.035, 95% CI -0.126 to 0.055), which equated to an improvement of 1 letter on the ETDRS chart. For people having placebo there was a worsening of the LogMAR (change +0.085, 95% CI -0.032 to 0.203), which equated to a worsening of 4 letters on the ETDRS chart. The between-group difference was not statistically significant (LogMAR -0.120, 95% CI -0.255 to 0.014; p=0.078) and equated to a 6 letter change. In the RHODOS trial, a higher proportion of people in the idebenone group (ITT 30.2%; n=16) than in the placebo group (ITT 10.3%, n=3) showed clinically relevant recovery (CRR) from baseline. The difference between the groups was not statistically significant (p=0.056). The committee noted that the statistically significant changes in the best VA and VA of the best eye from baseline did not reach statistical significance. It acknowledged that even a small improvement in vision would be important, particularly for people with severe sight impairment. The company explained that RHODOS was short and was completed before a wide understanding of the natural history of LHON. So, it may not have shown the true benefit of idebenone. It presented further non-randomised evidence from longer-term trials from EAP and LEROS. In EAP, there was a slight improvement in best VA. The LogMAR decreased from 1.23 (95% CI -0.18 to 1.80) at baseline to 1.19 (95% CI -0.16 to 1.80) at last visit. In LEROS, there was also a slight improvement in best VA from baseline to 24 months (ITT population). There was a mean change in the LogMAR of -0.09 in people with LHON onset in the second eye of 1 year or less and a change in the LogMAR of -0.19 in people with LHON onset in the second eye of more than 1 year. The committee concluded that the evidence suggested that idebenone may have some benefit in terms of improving vision, and preventing vision deterioration and progression of LHON. But it considered that the results were uncertain because of the non-randomised nature of the available long-term evidence.

Generalisability

3.8 The committee noted small differences in baseline characteristics such as age and sex between studies. The EAG's clinical experts considered that age at baseline and sex are not the prognostic factors for LHON, so this was unlikely to have affected the results. The EAG explained that people in the EAP and CaRS studies may not have been representative of UK clinical practice because their vision loss had started within in last 12 months. It explained that RHODOS included people with onset of vision loss 5 years or less, while vision loss in a large proportion of the UK LHON population started more than 5 years ago. The committee noted that both RHODOS and LEROS included people across various stages of LHON. LEROS represented the acute, dynamic and chronic phases while RHODOS primarily represented the chronic phase. It also noted that people in the EAP and CaRS studies represented the acute and dynamic phases. The committee was aware that the proportion of people with the m.11778G>A mutation was lower in LEROS compared with RHODOS, EAP and CaRS. It also observed that the CaRS studies included a larger proportion of people with m.11778G>A compared with RHODOS, EAP and LEROS. That mutation is associated with a poor prognosis and a lower probability of spontaneous improvement. The clinical experts considered that idebenone may have slightly more effect if used in the acute phase or before reaching nadir. They explained that the rate of spontaneous improvement that they have seen in clinical practice is lower than the rate reported in the literature. They also explained that the age of onset of vision loss is associated with spontaneous improvement, for example, young children will have greater chances of spontaneous improvement. The committee noted considerable uncertainty with the generalisability of the evidence. It considered the time from symptom onset, or an understanding of the phase of LHON (time from nadir), was likely an important factor that had not been clearly explored in all data sources.

Establishing relative treatment effect

3.9 A direct comparison between idebenone and standard care was only available for 6 months. After this, no direct evidence was available comparing idebenone with standard care. The company derived relative treatment effects of idebenone compared with standard care from an ITC using 2 unmatched populations. These were the EAP population for idebenone and the CaRS natural history studies. The EAG noted that the imbalance in prognostic factors between the EAP and the CaRS studies, for example, the study differences in the prevalence of 3 mutations. The EAG explained that this could have biased the result of the ITC. So, it considered that matching the idebenone and standard-care cohorts would be less biased. At the clarification stage, the company provided a propensity-score matching analysis (PSM) of changes in best VA between LEROS and CaRS 1 and CaRS 2 at month 24. The EAG considered after matching baseline characteristics were reasonably balanced between LEROS and CaRS 1 and CaRS 2. But it noted that the age of first symptom onset was younger in the standard-care cohort than the idebenone cohort. Also, the prevalence of T14484C genotypes was higher in the idebenone cohort than in the standard-care cohort. The EAG explained that only a limited amount of the CaRS follow-up data was included in the PSM analyses. This was because the company chose to only analyse a single visit pair (from baseline to 24 months), rather than all available data for standard care. The EAG explained that the median time between visits was 11.7 months in the CaRS studies. So, restricting the analysis to visit pairs 24 months apart likely did not use all the available data. It considered matching people between LEROS and the CaRS studies at baseline and using all available follow-up data in the analysis. The committee noted that the results of the ITC suggested that idebenone appeared to improve change in best VA at 24 months by -0.02 on the LogMAR scale. This meant it was slightly more effective than standard care in improving VA. But this was not statistically significant, which meant that it was likely that there was no evidence of a difference in treatment effect between idebenone and standard care. The committee

understood that PSM does not provide reliable evidence of the long-term treatment benefit of idebenone compared with standard care. But it considered there were substantial uncertainties in the methods of the ITC because of the limitations of the evidence and time in which it was completed. The committee considered that there was insufficient sensitivity analysis and exploration of uncertainty of the population adjustment used in the ITC. There were also considerable limitations in the methodology of only using patient-level data for beyond 24 months in the CaRS dataset. It requested analyses based on a more comprehensive view of the entirety of the available CaRS evidence. It noted, in particular, the importance of the trajectory of each person's best VA after any observed nadir and the stability of VA during that time period.

Economic model

Company's model structure

3.10 The company presented an economic model comparing idebenone with standard care. The model was based on a Markov state transition model that included 8 health states and an absorbing death state. Health states were based on VA expressed using the LogMAR (LogMAR less than 0.3, LogMAR 0.3 to 0.6, LogMAR 0.6 to 1.0, LogMAR 1.0 to 1.3, LogMAR 1.3 to 1.7.) counting figures, hand movement and light perception. The company explained that its model structure was in line with model structures used in NICE's highly specialised technologies guidance on voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations and NICE's technology appraisals guidance on ranibizumab for treating diabetic macular oedema, ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and ranibizumab for treating choroidal neovascularisation associated with pathological myopia. The model had a lifetime horizon (66 years) and 3-month cycle length, and people started at age 34 years (mean age in RHODOS). The EAG explained that health-related quality of life does not perfectly match gaining or losing sight.

Instead, specific abilities related to vision for example, being able to drive (less than LogMAR 0.3) or read certain letters on a LogMAR chart (LogMAR more than 1.7). The EAG also explained that the large number of health states in the company's model reduced the available patient data to inform each transition probability. This led to health-state transitions being impossible and multiple data imputations being needed. For example, under both probabilistic and deterministic conditions, it was not possible for people who had had idebenone to remain in the hand movement health state past cycle 10 (2.5 years) in the company's model. The EAG considered that the company's model was flawed because there was insufficient evidence to populate the transitions between the high number of health states in the model. So, the EAG preferred to use a simplified model with a lower number of health states (limited visual impairment, moderate visual impairment, visually impaired [on-chart] and visual impaired [off-chart]). The patient and clinical experts disagreed with the EAG's health states, particularly the lack of distinction between health states with lower VA. They explained that there are significant functional differences between being able to count fingers and just seeing hand movement. The committee heard that these differences will not be apparent by grouping all people as off-chart. The patient experts explained that being able to count fingers has practical implications for daily activities such as cooking, moving around the home and the ability to use devices. In contrast, relying only on hand movement perception severely limits independence and ability to perform daily activities. The patient and clinical experts agreed that the company's modelled health states captured health states more comprehensively. The committee agreed that the high number of health states but limited observed transitions increases the uncertainty of a model structure. But it also noted that transitions between counting fingers and states with higher VA would be associated with a significant benefit that would not be captured in a less sensitive model. The committee requested further analyses that show the sensitivity of the model to transitions, particularly for lower VA. It also

asked for analyses that explore the robustness of transition probabilities in both model structures. In particular, separating off-chart health states in the EAG model structure, especially for counting fingers VA, would be helpful.

Modelling idebenone long-term treatment effect

3.11 The committee was aware that the company used the RHODOS study to inform the treatment effectiveness for both idebenone and standard care for 6 months. It noted that the company preferred to use the EAP to derive a long-term treatment effect for idebenone after RHODOS. The company clarified that it had preferred to use the EAP over LEROS because of less heterogeneity within EAP and had a longer study duration. It explained that the proportion of boys and men, and the genetic distribution of the EAP was more aligned with RHODOS than LEROS. The data is considered confidential by the company and cannot be reported here. The company also explained that the outcomes of RHODOS and the EAP were also similar. In RHODOS, 30.2% of people who had had idebenone had CRR at 6 months. In the EAP it was 46.0% of people. The EAG explained that it does not consider CRR to be a relevant indicator of improved health-related quality of life. This is because it does not differentiate between sight recovery and functional sight recovery. The EAG noted that the LEROS data was more comparable to RHODOS than the EAP, with fewer people having CRR in LEROS compared with the EAP and RHODOS. The EAG explained that LEROS involved more people (196 compared with 87 in the EAP). This meant higher chances of having more data to inform the transitions between the health states. The EAP included people with symptom onset within 1 year, while LEROS included people with symptom onset within 5 years. This aligned with RHODOS. The EAG noted that 44% of people in LEROS had symptom onset for more than 1 year, spontaneous improvement might be more likely in the EAP than LEROS after nadir. This confounded the estimated treatment effect in the EAP. So, the EAG preferred to use LEROS to inform idebenone's treatment effect after RHODOS. The committee

concluded that the EAG's approach of using LEROS data to model idebenone long-term treatment was more appropriate for decision making.

Modelling the long-term treatment effect of standard care

3.12 The committee noted that the company used a similar approach (natural history CaRS 1 data) to supplement the RHODOS data after 6 months for standard-care treatment effectiveness in the model. The company explained that the baseline characteristics (age, sex and mutation) of the natural history population in CaRS 1 were similar to those in RHODOS. The company also compared the proportion of people who had CRR at 6 months in RHODOS and CaRS 1 with 10.3% of people having placebo in RHODOS and 8.1% of people in CaRS 1. So, the company considered CaRS 1 was appropriate to model standard-care treatment effectiveness after RHODOS. The EAG noted that the company used a last observation carried forward (LOCF) approach to address missing data. This assumed that people remained in their last observed health states when new data was not available. The EAG noted that using CaRS 2 or combining the CaRS 1 and 2 studies would have provided more robust estimates of standard-care treatment effect. The EAG explained that using a larger CaRS 2 study or a combination of CaRS 1 and 2 could reduce the extent of missing data imputation needed, and the need for LOCF. At the clarification stage, the EAG requested a scenario using the EAG's preferred model health states while removing standard-care observations generated using LOCF. The EAG explained that, in the company's scenario, all transition probabilities were informed using only 169 observations. This was compared with the 740 observations when using CaRS 1 and LOCF. The EAG explained that, in the company's base case, almost 50% of the observations for standard care were informed by LOCF at 6 months and this was 90% at 21 months. The EAG considered the standard-care treatment effect in the scenario was underestimated and was highly uncertain because only a small part of the data was used. It also considered that the model outcomes did not align with the clinical outcomes. So, the EAG requested the company to do scenarios using:

- all appropriate CaRS 1 and 2 observations available
- the matched natural history data from the CaRS studies and the idebenone LEROS population
- only RHODOS-OFU to model long-term treatment effects.

The committee was aware that the company did not provide the requested scenarios. To address this, the EAG provided an alternative scenario using the idebenone transition probabilities from LEROS to model standard care after RHODOS. This was because the RHODOS-OFU study showed a maintained difference in change in the LogMAR from the end of RHODOS (6 months) to the end of RHODOS-OFU (30 months) between idebenone and standard care. The committee noted that standard-care mean change in the LogMAR using the LEROS transition probabilities scenario aligned more closely to the RHODOS-OFU results compared with the company's base case. But it also noted the limitations of using transition probabilities from the idebenone arm to describe standard care. The committee also noted that the company's approach to using the CaRS studies with LOCF was highly uncertain. This was because it did not replicate the clinical trial findings in the model. The committee concluded that there were difficulties with using both the company's and EAG's approaches to modelling standard care. It noted that the cost-effectiveness estimates were very sensitive to the approach to modelling long-term standard care because these results were extended over a very long time horizon. It did not consider that this uncertainty had been fully explored with the sensitivity analysis available. It requested further scenarios using alternative assumptions giving a holistic view of all available sources of evidence for change in VA. It considered the multiple imputation method over LOCF more appropriate to handle missing data. The committee noted that the company model lacked the functionality to explore the uncertainty of relative treatment effect in its probabilistic analysis. It considered that extensive sensitivity analyses should be done in the absence of the ability to explore this uncertainty.

Time on treatment

3.13 The committee noted that both the company and the EAG assumed that people would stay on idebenone for up to 3 years. The company used pooled time on treatment data seen in RHODOS and the EAP to model time on treatment with idebenone. The committee noted that clinical opinion received by the EAG suggested that people may continue to have idebenone for more than 3 years if LHON responds to idebenone or has only recently stabilised. The committee noted that the company considered extrapolating beyond 3 years to be highly uncertain and inappropriate. This was because of a lack of data because of the small number of people who had treatment for more than 3 years. The patient experts mentioned that they expect idebenone to be used until LHON stabilisation. The clinical experts explained that, in clinical practice, they would use idebenone for up to 2 years if LHON is responding or until LHON stabilisation. They explained that, based on the evidence from the natural history studies and RHODOS, cell death does not continue in LHON for the rest of a person's life. People with LHON do not have repeated episodes of cell death, either with or without treatment over time. The committee was aware that treatment duration ranged from 2.4 to 70.4 months in the EAP study. The committee noted that, in clinical practice, people may have idebenone for longer than 3 years and that this would likely be driven by LHON stabilisation. The committee concluded that time on treatment for idebenone was uncertain. It added that it would like to have seen further sensitivity analyses using alternative assumptions from expected use in clinical practice (for example, using assumptions about stability from the available clinical data).

Health-related quality of life

3.14 In RHODOS, health-related quality-of-life data was collected using the Visual Function Index (VF-14), Clinicians Global Impression of Change and energy levels. The committee was aware that the NICE reference case recommends using EQ-5D-3L directly measured from people with a

condition. When EQ-5D-3L is not available from clinical trial data, EQ-5D data can be sourced from published literature or estimated by mapping from other measures of health-related quality of life collected in clinical trials, using published mapping algorithms. The company explained that no published mapping algorithm was available to map from VF-14, collected in RHODOS, to the EQ-5D. So, it used health-state utility values from Brown et al. (1999) derived from using time trade-off valuation from 325 people with vision loss caused by a range of vitreoretinal conditions. Most people had age-related macular degeneration (33%) or diabetic retinopathy (33%). This was in line with NICE's highly specialised technologies guidance on voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations and NICE's technology appraisals guidance on ranibizumab for treating diabetic macular oedema, ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and ranibizumab for treating choroidal neovascularisation associated with pathological myopia. The committee noted that the company also provided scenarios using alternative utility values identified by Lawrence et al. (2023), Czoski-Murray et al. (2009) and Rentz et al. (2014). The EAG explained that utility values from Brown et al. (1999) were not based on EQ-5D-3L, and had a higher average age than people with LHON, US-based population. So, the EAG preferred to use utility values from Lawrence et al. (2023) in its base case. In this study, EQ-5D data was collected from people in the UK with LHON with an average age of 46.5 years. The committee noted that the source of utility values had a minimal effect on the cost-effectiveness results in the EAG's base case. But it noted that this could have been, in part, because of the alternative model structure used by the EAG. The committee concluded that Lawrence et al. (2023) was a more appropriate source to derive utility values from. It added that it would like to see further scenarios explored using varying utility values, in particular for reflecting a counting-fingers health state.

Carer disutility

3.15 The committee noted that the company applied a utility decrement of 0.04 in line with NICE's highly specialised technologies guidance on voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations for all people with a LogMAR of more than 1.0 to represent the disutility associated with LHON caregivers health-related quality of life. The clinical and patient experts explained that most people with LHON need constant support from family members and carers. A patient organisation submission highlighted that a child's diagnosis can have a significant effect on some parents' mental and physical wellbeing. The committee noted there may be effects on carers' quality of life, particularly for younger people with LHON. But it highlighted that the reference case refers to health-related quality of life as a result of LHON. So, it may be difficult to interpret this in the context of adults with LHON that live independently without fulltime carers. The committee noted that it had not been presented with evidence for carer quality of life associated with LHON. It also noted that NICE's highly specialised technologies guidance on voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations considered that it was appropriate to apply carer disutilities for parents of children with a condition that causes blindness. But this was not applied to adults. So, it concluded that the EAG's approach of excluding disutility values for carers of adults in all health states could be appropriate, but it could consider scenarios including a carer disutility for adults with LHON if more quantitative evidence for carers of adults with LHON or other conditions that cause blindness was provided.

Health-state resource use

3.16 The committee noted that the company included resource costs for each health state, assuming costs associated with blindness using Mead et al. (2003). It included costs of hospitalisations (assumed to be because of injurious falls), outpatient visits (obtaining low-vision aids and rehabilitation), blind registration, supportive living, residential care (aged 65 years and over) and depression. Blind registration and depression

were assumed to be one-off costs applied in the first year, whereas all other costs are assumed to occur per cycle. The company explained that Meads et al. (2003) was not specifically based on people with LHON. It also had an older population who were classed as blind, so the reported resource use did not apply to the LHON population. So, it got estimates of each resource across the included model health states (on-chart), classified by the LogMAR value, from a survey done with 3 international ophthalmologists. These estimates were validated by the 5 UK clinical experts. The EAG noted uncertainty in the estimates provided by the experts. For example, a wide range between the highest and lowest estimates was provided for many resource categories. The EAG noted that 1 expert said that they would not expect young people with vision equal to driving vision to fall regularly, as estimated by the company's resource use. The EAG explained that, in clinical practice, people who would incur health resource costs would be clinically visually impaired with a LogMAR of 1.0 to 1.3. So, the EAG only applied resource costs to people with a LogMAR of more than 1, except depression costs, which were assumed to apply to all health states. The clinical experts explained that they would expect costs for outpatient visits for low-vision aids and rehabilitation for people with a LogMAR of less than 1. The committee noted that although there were significant differences in the approaches used by the company and the EAG regarding the use of health-state resource utilisation, this had a minor impact on the cost-effectiveness results. It concluded that it was appropriate to apply the resource costs of outpatient visits (obtaining low-vision aids and rehabilitation) for health stages with a LogMAR of less than 1.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 The committee noted that the company's deterministic base case gave an incremental cost-effectiveness ratio (ICER) below £20,000 per quality-adjusted life year (QALY) gained for idebenone compared with standard

care. The EAG made several changes to the company's base case. These changes increased the cost-effectiveness estimates to a level that was above what NICE normally considers an acceptable use of NHS resources. The committee noted that the EAG's deterministic base case showed that ICERs for idebenone compared with standard care were over £100,000 per QALY gained. The committee considered the cost-effectiveness results when using the company's and EAG's base cases. The committee was also presented with a range of scenarios investigating the impact of different assumptions on the company's base case. The committee noted the high level of uncertainty in the model, particularly concerning:

- the ITC using the PSM method, which was highly uncertain, with alternative methods explored (see section 3.9)
- the high number of health states with insufficient evidence, and issues with the model such as a lack the functionality to allow idebenone and SoC transition probabilities to vary according to treatment effectiveness (see section 3.10)
- the uncertainties in the modelling of standard-care treatment effect (see section 3.12)
- modelled time on treatment for idebenone uncertainty, with sensitivity analyses to be explored (see section 3.13)
- utilities values that were not LHON and UK specific (see section 3.14)
- the carer disutility assumption used in the base case (see section 3.15).

Acceptable ICER

3.18 NICE's manual on health technology evaluation notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee was aware that it may accept a higher degree of uncertainty when evidence generation is particularly

difficult because the condition is rare. It noted that several of the key uncertainties were affected by the rarity of LHON. These included limited evidence on the long-term effects of idebenone and the assumption used to model the standard-care treatment effect. So, the committee concluded that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (around £30,000 per QALY gained).

Other factors

3.19 Because of the rarity of LHON, the committee recognised difficulties in the ability to collect or generate clinical evidence on idebenone's comparative effectiveness and the natural history of LHON. It agreed that this contributed to significant uncertainty in decision making. The committee also noted that there may be other factors not included in the analysis. These included the potential of idebenone to reduce anxiety and depression, and the effect of LHON on education and career opportunities from vision loss. It considered that it could potentially apply greater flexibility in decisions around acceptance of uncertainty and consideration of benefits outside of the ICER calculation in these circumstances. But the committee was mindful it should be cautious in accepting a higher degree of uncertainty when the highest standard of evidence generation that should be expected in the circumstances had not been achieved. Because it considered that additional analyses would be possible to reduce these uncertainties, it concluded it was not appropriate to increase its flexibility.

Equalities

3.20 The committee was aware that the population for which idebenone is indicated included young people and adults. The committee noted that LHON is a genetic condition. It was aware that LHON is a devastating condition that can begin at a very young age and that people with the condition, and their families and carers, are affected in all aspects of life (see section 3.2). The committee agreed that, if idebenone were

recommended, the recommendation would not restrict access for some people over others. No other equality or social value judgement issues were identified.

Innovation

3.21 The clinical experts considered idebenone to be innovative for treating LHON in people with a very high unmet need. The clinical experts also considered idebenone a step change for LHON treatment because it has the potential to make a difference in health-related quality of life. They explained that, with idebenone, about 50% of people will have the opportunity of a better visual outcome. The committee acknowledged the benefits offered by idebenone and heard from the clinical and patient experts that idebenone could offer wide-ranging effects including:

- reduced anxiety and depression
- independence with daily activities
- increased socialising
- improved mental health
- rebuilding confidence
- better education and career opportunities.

The committee considered the uncertainties in the evidence meant that it was unclear whether these had been fully captured in the model. It concluded that it had not been presented with evidence of any additional benefits specific to idebenone that had not been captured in the QALY measurement.

Conclusion

Recommendation

3.22 The committee's concerns about the clinical evidence and the cost-effectiveness model meant that it was not confident about the results presented and so was unable to identify a plausible ICER. It concluded

that it would like the uncertainties to be addressed and that idebenone could not be recommended.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas
Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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