MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP

Agenda Item No	
National Programme	Trauma
Clinical Reference Group	Specialised Ear and Ophthalmology Services
URN	URN 1810

Title
Idebenone for Leber's Hereditary Optic Neuropathy in patients over 12 years of age

Actions Requested	1. Agree the policy proposition
	2. Recommend its approval as an IYSD and not for routine commissioning.

Proposition
Not for routine commissioning **Associated clinical commissioning documents** None

Clinical panel recommendation
When they first reviewed the evidence in October 2018, Clinical Panel recommended that the policy progress as a not-for-routine commissioning policy proposition based on the evidence available and having assessed the degree of benefit attributable to idebenone as modest at best, with a high degree of uncertainty. When the policy was reviewed again by Clinical Panel in January 2019, the comments from the Policy Working Group (PWG) were noted in relation to Leber's Hereditary Optic Neuropathy (LHON) being a rare condition and that the main randomised control trial was relatively small (55 patients receiving idebenone and 30 receiving placebo, with outcomes measured at 24 weeks). The primary visual acuity outcomes favoured treatment but were not statistically significant. Panel also noted the feedback from the PWG in relation to treatment may be more effective in recent onset disease and that the benefit seen in patients with discordant vision (which tends to occur earlier in the disease process) supports

this view. However, no specific trial evidence was provided to support this. Clinical Panel therefore supported the not for routine commissioning policy proposition.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	

10.	Safety	Descriptive data on the safety and tolerability of idebenone was collected for all patients in the main study (RHODOS) and the expanded access programme (EAP). In RHODOS idebenone was well tolerated with most adverse events mild or moderate. The two serious adverse events reported (1 idebenone, 1 placebo) were considered unrelated to the treatment. No deaths were reported in RHODOS. Similar findings were found in EAP data reported in the EPAR. Results suggest idebenone was well-tolerated and considered safe at both 24 weeks follow-up and longer-term (during the EAP, patients received treatment for a mean treatment duration of 23.8 months). The EPAR noted the available safety profile for idebenone was considered benign with the majority of AEs being mild or moderate and few reports of serious AEs. However, the EPAR noted available safety data in the target population were limited. It is important to note that RHODOS included a relatively small population of people at various stages of disease progression. Longer term evidence from the EAP was limited to a small population, where people received idebenone but decisions on the prescribed dose and length of treatment were made by their doctor. These studies therefore provide limited evidence on the long-term safety of idebenone.
11.	Delivery of intervention	

Other health outcome measures determined by the evidence review		
No	Outcome measure	Summary from evidence review
1.	Visual acuity	Visual acuity (VA) is the ability to see objects clearly and is also known as clarity of vision. It is an important measure of visual function, although it does not define the full experience of vision. In all studies, VA was measured using a chart known as the Early Treatment Diabetic Retinopathy Study (ETDRS) chart; or converted values from Snellen charts. Both are used to

		identify the number of letters a person can read on a standardised chart. The number of letters is expressed using logMAR values. LogMAR quantifies vision 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). A person “off-chart” has vision worse than 1.68 and VA is measured by counting fingers or light perception. The ETDRS chart includes 6 rows with 5 letters on each row. Each row of letters decreases in size. Every letter on the chart has a value of 0.02 log units. If a person was able to read all letters on a specific line correctly, they would score a maximum of 0.1 log units (i.e. 0.02 per letter multiplied by a maximum of 5 letters per row). The logMAR score reduces by -0.02 log units for every additional letter the patient is able to read correctly on the following lines of the chart. The best evidence came from RHODOS (a 24-week phase II randomised placebo-controlled trial, n=85 in people aged 14 years and older with LHON). The primary outcome of best recovery/ least worsening in VA measured the best recovering VA in either right or left eye (whichever showed best improvement) at 24 weeks. Results showed a mean 3 letter improvement at 24 weeks follow up for idebenone vs placebo, however this was not statistically significant (p=0.291) which means it is not possible to state with certainty that this result was directly due to the effects of receiving idebenone. A number of secondary measures of VA were also presented in the data, with subgroups, and alternative ways of measuring VA. These included the change from baseline in VA of the patients best seeing eye (which looked at the patient’s change in vision in either right or left eye over the study period); change from baseline in best VA (which compared the patient’s best seeing eye at baseline with their best seeing eye at end-point, even if these were not the same); and looking at the VA of both eyes combined. These outcomes were thought to be relevant to consider the patient’s overall ability to see.

		• Although the change from baseline in best VA (either eye) was not statistically significant, the change from baseline of VA (both eyes combined) showed a statistically significant improvement for idebenone vs placebo (estimated difference between groups = logMAR -0.100; 95% confidence that the true effect lay between logMAR -0.188 to logMAR -0.012; p = 0.026). This suggests there is a high probability that this difference was a result of directly receiving treatment. • Change from baseline VA of the best seeing eye at baseline was not statistically significant. • A post-hoc sub-analysis for people with discordant VA at baseline (people who had varying quality of vision in each eye, described as a difference of more than logMAR 0.2 between eyes) showed a statistically significant improvement for idebenone vs placebo for all primary and secondary outcomes. • VA was also assessed by counting the number of patients and eyes whose VA improved by the ability to read at least 2 rows of letters on the logMAR scale; or people whose VA improved from being unable to read any letters on the scale to the ability to read at least one letter on the scale. This was defined as people who had a clinically relevant recovery (CRR). The EPAR showed a statistically significant improvement in CRR in favour of idebenone with 21 eyes (19.8%) in 16 people receiving idebenone and in 2 eyes (3.6%) in 2 people in the placebo group (p=0.0041) achieving a CRR at 24 weeks. • RHODOS-OFU (a longer term follow-up of RHODOS, where patients did not receive further treatment with idebenone) found no difference between groups in VA of best eye from either baseline or endpoint of RHODOS to time of OFU visit (a mean of 30 months). The EPAR stated that the between group difference was maintained, “suggesting that the benefit obtained with idebenone after 6 months treatment

		persisted even after withdrawal of treatment". Taking all of the above into account, results suggest that idebenone improved VA compared with placebo, however results were not always statistically significant for the whole population. Statistically significant improvements in VA were shown in some subgroups, including those with discordant vision. Results should be interpreted with caution because the RHODOS trial was a phase II design of a relatively small population of people at various stages of disease progression with a short follow-up and therefore provides limited evidence on the long-term benefits of idebenone. Some analyses used a modified ITT (mITT) population where a person with spontaneous recovery was excluded from results (as they were deemed a confounder; that is, a variable other than treatment effect which may be influencing the results). The EPAR stated there was a risk of over-estimating the effect of idebenone "because of potential for spontaneous recovery in LHON" and 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 a considerable increase in differences between the intervention and comparator groups.
2.	Colour contrast sensitivity	Colour contrast sensitivity tests measure the ability to distinguish between certain colours, and shades of light versus dark colours. In the studies this was measured by assessing any colour confusion (colour vision deficiency) between protan (red-green) and tritan (blue-yellow) colour vision. The difference between treatment groups was presented as a percentage change, where a negative value showed an improvement in colour vision. The best evidence came from RHODOS where a sub-population (n=39) were assessed for protan (red-green) and tritan (blue-yellow) colour confusion. Results showed there was a statistically significant improvement of tritan colour vision for idebenone compared with placebo at both 12 weeks follow-up (difference

		between groups: -14.51% improvement; with 95% confidence that the true effect lay between -24.19% to -4.83% p = 0.004) and 24 weeks follow-up (difference between groups: -13.63% improvement; with 95% confidence that the true effect lay between -23.61% to -3.66%; p = 0.008). Changes in protan colour contrast showed improvements but were not statistically significant at either 12 or 24-week follow-up (p=0.239). Supportive evidence came from a post-hoc analysis of a sub-set of data originally assessed in RHODOS (Rudolph et al. 2013). This showed a statistically significant difference in favour of idebenone in the change of protan and tritan colour contrast sensitivity, for people with discordant VA at baseline at both 12 and 24-weeks follow-up. When the data was further analysed by age of patient, the difference between treatment groups was statistically significant for tritan colour contrast for people who were younger than 30 years at baseline at both 12 and 24 weeks. Results suggest idebenone may be effective in improving or preserving colour vision, especially in the subgroups of people with discordant VA (conflicting visual abilities in either eye), and people younger than 30 years. Results should be interpreted with caution, as these were based on a small sub analysis of people originally completing the RHODOS trial, which means it is very hard to generalise to a wider population analysis. RHODOS also had a short follow-up and therefore provides limited evidence on the long-term benefits of idebenone therapy.
3.	Health related quality of life	Quality of life was measured using 2 validated quality of life questionnaires, the Visual Function Index (VF-14) and the Clinician's Global Impression of Change (CGIC). The best evidence came from RHODOS, at 24-weeks follow up, where the change from baseline in VF-14 scores was assessed in a sub-set of patients. At 24-week completion there was no difference in scores between people receiving idebenone or people receiving placebo (P=0.577). Similar findings were reported in the

		RHODOS-OFU where differences were small and not statistically significant. Statistical analyses were not reported for CGIC scores during RHODOS, however, the scores from the idebenone group and placebo group were similar when recorded at 24-weeks follow-up. The EPAR notes that these results suggest that any potential improvement in vision in patients treated with idebenone did not convert into benefits for the patient's daily activities and health-related quality of life. Although the overall benefit of idebenone to health-related quality of life currently remains unclear, it is important to note that the RHODOS trial included a relatively small, population of people at various stages of their disease progression with a short follow-up and therefore provides limited evidence on the long-term benefits of idebenone therapy.

Considerations from review by Rare Disease Advisory Group
Not Applicable

Pharmaceutical considerations
The policy proposition does not recommend idebenone for treating people over 12 years of age with Leber's Hereditary Optic Neuropathy, in line with the product licence. It is excluded to tariff.

Considerations from review by National Programme of Care
The proposal received the support of the Trauma PoC Board on 1 October 2019