Cost-effectiveness of idebenone (Raxone®) for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON)

The NCPE has issued a recommendation regarding the cost-effectiveness of idebenone (Raxone®). Following assessment of the applicant's submission, the NCPE recommends that idebenone (Raxone®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Santhera (UK) Limited) economic dossier on the cost effectiveness of idebenone (Raxone®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **August 2018**

Summary

In November 2017, Santhera (UK) Limited submitted a dossier examining the clinical, safety and economic evidence in support of an appraisal of the cost-effectiveness and budget impact of idebenone (Raxone®) for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON). LHON is a rare mitochondrial disease of the eye, caused by one of three main mutations in mitochondrial DNA. The disease predominantly affects males, with onset usually occurring in early adulthood and it results in a sudden deterioration in vision. Final data submitted by the applicant was received on 22nd June 2018. Santhera (UK) Limited are seeking reimbursement for idebenone on the High Tech Drug Scheme (HTDS).

Idebenone is a short-chain benzoquinone derivative and a synthetic analogue of ubiquinone (co-enzyme Q10). Idebenone exerts antioxidant properties and by inhibiting lipid peroxidation may be able to protect cell membranes and mitochondria from oxidative damage. It is thought that idebenone may re-activate viable-but-inactive retinal ganglion cells in LHON patients. The recommended dose of idebenone for LHON is 900 mg/day orally (300 mg, three times a day) and there are no data regarding continuous treatment with idebenone beyond 6 months. Idebenone is formulated as 150mg film-coated tablets and should be administered with food to increase its bioavailability.

As there are no other licensed treatment options available for LHON, it is anticipated that idebenone will be used as first-line therapy within its marketing authorisation.

1. Comparative effectiveness of idebenone

The applicant presented data for the efficacy of idebenone from the pivotal Phase II double-blind, randomised, placebo-controlled study RHODOS. Results from RHODOS are further supported by the single visit observational follow-up study RHODOS-OFU and data gained from an Expanded Access Programme (EAP) and data gathered in the form of a historical case record survey (CRS).

In RHODOS a total of 85 LHON patients, 14-66 years of age, with any of the 3 primary mtDNA mutations (G11778A, G3460A or T14484C) and disease duration of not more than 5

years were enrolled. Patients were randomised to receive, in a 2:1 ratio, treatment with idebenone 300mg three times a day (n=55) or placebo (n=30) for a period of 24 weeks. The primary endpoint "best recovery of visual acuity (VA)", expressed as logarithm of the minimal angle of resolution (logMAR) values was defined as the result from the eye experiencing the most positive improvement in VA from baseline to week 24 using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. The main secondary endpoint "change in best VA" was measured as the difference between best VA in either the left or right eye at 24 weeks compared to baseline. The logMAR scale ranges from 0.0 (normal vision) to 1.68 (able to read only one large letter correctly from a distance of one metre). One vision chart letter is approximately equivalent to -0.02 on the logMAR scale. In RHODOS, logMAR ≥1.0 was used as a proxy for being legally blind. Patients who could not see ETDRS letters at all ("off-chart" patients) and who were only able to count fingers, detect hand motion or light perception, were assigned logMAR values 2.0, 2.3 and 2.6, respectively. Efficacy analysis was performed in the intention to treat (ITT) population, (n=82). Although defined as all randomised patients who received at least one dose of the study medication, three randomised patients who had received study medication were excluded prospectively from the ITT population for all VA analyses due to inaccurate recordings in VA measurements either at baseline or at week 24.

The primary endpoint of RHODOS was not achieved. Although a numerical improvement approximately equivalent to three ETDRS letters was achieved, there was no significant difference between the treatment groups. There was also no significant difference between treatment groups for the key secondary outcome of mean change from baseline to week 24 in best VA at week 24 compared with best VA at baseline, or in change in VA of the eye that was better seeing at baseline. When data from all 164 eyes were combined, there was a significant improvement in mean VA at 24 weeks for idebenone compared with placebo. (See Table 1).

Table 1: Primary and main secondary endpoints from the RHODOS trial for the ITT population from baseline to week 24

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI)** [estimated change in letters]	**p-value**
	Idebenone (n=53)	**Placebo (n=29)**		
Primary endpoint: Best Recovery in VA				
ITT, Week 24	-0.135 (-0.216, -0.054) [+6 letters]	-0.071 (-0.176, 0.034) [+3 letters]	-0.064 ± 0.061 (-0.184, 0.055) [3 letters]	0.291
Key secondary endpoint: Best VA at Week 24 (best eye at Week 24) compared to best VA at Baseline (best eye at Baseline)				
ITT, Week 24	-0.035 (-0.126, 0.055) [+1 letter]	0.085 (-0.032, 0.203) [-4 letters]	-0.120 ± 0.068 (-0.2546, 0.0137) [6 letters]	0.078
Secondary endpoint: Change in visual acuity of the best eye				
ITT, Week 24	-0.030 (-0.120, 0.060) [+1 letter]	0.098 (0.020, 0.215) [-4 letters]	-0.128 (-0.262, 0.006) [6 letters]	0.061
Secondary endpoint: Change in visual acuity for all eyes				
ITT, Week 24	-0.054 (-0.114, 0.005) [+ 2 letters]	0.046 (-0.032, 0.123) [-2 letters]	-0.100 (-0.188, -0.012) [5 letters]	0.026

A pre-specified analysis in RHODOS determined the proportion of patients with an eye with baseline VA of ≤0.5 logMAR in whom the VA deteriorated to ≥1.0 logMAR. In this very small subgroup of patients (n=8), 0 of 6 patients in the idebenone group deteriorated to ≥1.0 logMAR whereas 2 of 2 patients in the placebo group showed such a deterioration. There was no significant difference between treatments in terms of quality of life.

In a single-visit observational follow-up study, RHODOS-OFU, VA assessments from 58 patients (n=39 idebenone, n= 19 placebo) obtained at a median of 30 months after the end of the 24 week RHODOS treatment period, indicated that the effect of idebenone may be maintained (but did not reach statistical significance). Some patients had taken idebenone in the intervening period.

A post-hoc responder analysis was performed in RHODOS evaluating the proportion of patients who had a clinically relevant recovery (CRR) of VA from baseline in at least one eye,

defined as either: (i) improvement in VA from unable to read a single letter to able to read at least 5 letters on the ETDRS chart; or (ii) improvement in VA by at least 10 letters on the ETDRS chart. Results are shown in Table 2 including supporting data from 62 LHON patients using idebenone in an EAP and from 94 untreated patients in a CRS.

Table 2: Proportion of patients with clinically relevant recovery of VA after 6 months from baseline

RHODOS (ITT)	**RHODOS idebenone (N=53)**	**RHODOS Placebo (N=29)**
Responders (N, %)	16 (30.2 %)	3 (10.3 %)
EAP and CRS	**EAP-idebenone (N=62)**	**CRS-untreated (N=94)**
Responders (N, %)	19 (30.6 %)	18 (19.1 %)

In a 2015 analysis of the EAP, the number of responders increased with longer treatment duration, from 19 out of 62 patients (30.6%) at 6 months to 17 out of 47 patients (36.2%) at 12 months. Additional, more recent analyses of the results from the EAP, after a mean treatment duration of 23.8 months show that the proportion of responders increased with treatment duration to 47.1% (41 out of 87 patients).

The CRS provided natural history data for 106 LHON patients with a known date of symptom onset who were assessed ≤ 2 years after this and had no recorded idebenone use. VA as a function of time since onset of symptoms was the primary outcome. 61% of eyes were already legally blind at presentation, of which 22% had already deteriorated to "off chart" VA. At nadir 96% of eyes were legally blind and 75% had deteriorated to off-chart VA. Over 50% of eyes deteriorated to logMAR ≥ 1.0 within 1 week of disease onset, increasing to over 70% within 3 months. By 12 months over 80% of patients' eyes were legally blind. After a mean 14.9 months since disease onset, 83% of the patients remained blind. An analysis of spontaneous CRR (sCRR) in 74 patients found that overall, sCRR in VA from nadir was observed in at least one eye of 23 out of 74 patients (31.1%), and in 36 out of 148 eyes (24.4%). The mean time from disease onset to spontaneous CRR was 9.9 months. A higher proportion of sCRR was observed in patients carrying the G3460A (50.0%, 6/12) and T14484C (42.9%, 3/7) compared to patients carrying the G11778A mutation (25.5%, 14/55).

2. Safety of idebenone

In the RHODOS study, the majority of subjects had at least one adverse effect (AE) (89% for idebenone and 87% for placebo). Overall, the incidence of all AEs and treatment related AEs were low and similar or lower on idebenone compared with placebo. AEs reported by ≥ 10%

of subjects on idebenone were: nasopharyngitis (25.5%), headache (23.6%), and influenza, increased blood triglycerides and cough (10.9% each). Headache, nasopharyngitis and cough were more frequent in the idebenone group than the placebo group. In addition, dizziness was reported at a higher incidence in subjects receiving idebenone (5.5%) compared to subjects receiving placebo (0%). Left ventricular hypertrophy (LVH) was reported for four subjects (7.3%) on idebenone but was not reported in the placebo group.
Five patients experienced treatment-related AEs: one each of elevated blood triglycerides, LVH, Wolff-Parkinson-White syndrome and abnormal liver function test in four patients in the idebenone group and elevated blood triglycerides plus abnormal liver function test in a single patient in the placebo group. No deaths occurred in the RHODOS study. No new safety concerns arose from the limited data presented in the RHODOS-OFU study.
Additional safety information from the EAP was consistent with that seen in previously reported studies.

The EMA was of the view that data on the clinical safety of idebenone under normal conditions of use could not be considered comprehensive, mainly due to the rarity of LHON disease and considered it necessary to generate additional safety data through a non-interventional post-authorisation safety study (PASS). The EMA requested the establishment of a drug exposure registry of patients prescribed idebenone for LHON in clinical practice, to generate data on long-term effectiveness and to address safety concerns including long-term safety and use in populations not studied in clinical trials. The EMA will review any new information which may become available annually and will update the Summary of Product Characteristics as necessary.

3. Cost effectiveness of idebenone

Methods

A de novo cost-utility analysis comparing idebenone with standard of care (SoC), in adult patients with LHON, was undertaken. The Health Services Executive (HSE) perspective and a lifetime time horizon were used, with a cycle length of three months. Half-cycle corrections were appropriately applied. The efficacy and safety inputs were derived from the clinical trials (RHODOS study, EAP study and CRS study). The time horizons of these pivotal trials

were significantly shorter than that of the model, and so considerable assumptions were used within the model.

The Markov model consisted of nine health states. The logMAR score quantifies visual acuity and defined the first five health states. The CF, HM, LP health states defined much lower levels of visual acuity than described by logMAR. An absorbing death state was also included. There were a large number of transition probabilities within this Markov model, with these probabilities being informed by a small number of patients and there is likely to be a significant proportion of these transitions being informed by very small numbers. Given the rarity of LHON, these small trial numbers are to be expected, but using these small numbers to create a complicated network of transition probabilities introduces significant uncertainty into the model. A key assumption in the Company's model was that patients remain in the health state that they are in at 36 months for the remaining duration of the time horizon, until they move to the absorbing death state. This is a very strong assumption and includes the most optimistic scenario where patients retain all benefits from their treatment for the remainder of their lifetime. The RG requested the company, in the preliminary questions, to include scenarios where the model structure is adjusted so that patients' can deteriorate and additional treatment cycles are required.

Utility values were derived from Brown et al (1999), where utility values were collected from patients using the time trade-off utility assessment method (along with standard gamble and a modified VF-14 questionnaire). This study was identified through a non-systematic literature review, the details of which have not been presented. The utility values were presented based on the logMAR equivalents to Snellen visual acuity states. These did not match up perfectly for each health state and therefore, some assumptions were made on the most appropriate value to choose from Brown et al.(1999). The RG were concerned that the patients being assessed in Brown et al (1999) were not an equivalent group of patients to LHON patients, and that the utility values of these older patients with potential co-morbidities from their underlying conditions, may not be appropriate to estimate utility values for this submission. However, there are very limited appropriate sources of utility estimates for this population, and given that this study has been used in several previous

technology appraisals for a range of diseases, it is likely to be the most appropriate source available.

Healthcare resource use data were derived from the RHODOS trial. The company also conducted a systematic review of the literature to identify resource use estimates and costs. One study was identified, however, this was deemed not applicable as the study was based in Germany. The costs included in the model were drug acquisition costs, and medical costs relating to blindness. Societal costs were also included, within a scenario analysis. Costs associated with adverse events were not included, with the company stating that this was due to the benign safety profile of idebenone. The treatment costs were calculated by multiplying the acquisition cost of treatment by the compliance and persistence of idebenone, derived from RHODOS and EAP studies. The persistence data from the trials was considered up to three years, after which it was assumed that all patients discontinued treatment. The company's submission assumed that patients only received one course of treatment with idebenone. The RG were concerned that multiple courses of treatment may be required for some or all patients receiving idebenone, with the current model underestimating the costs to the HSE. The review group asked for scenario analyses to be conducted. All of the scenarios increased both the price and ICER values.

Results

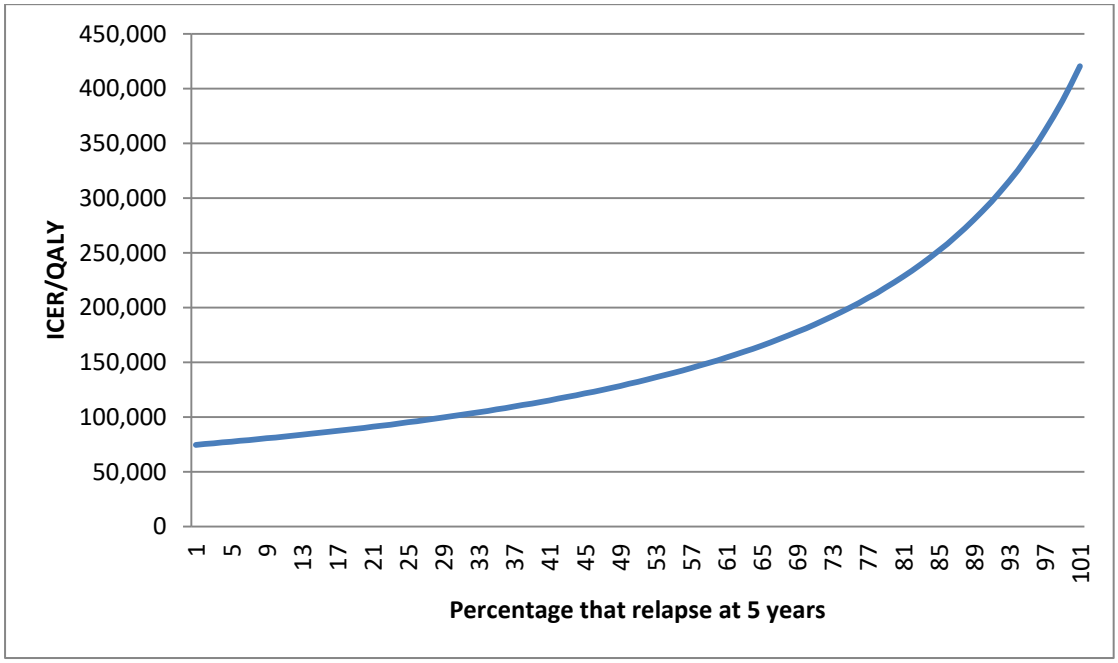
The company conducted an incremental analysis comparing no treatment to treatment with idebenone. The results of both a deterministic analysis and a probabilistic analysis, using 10,000 iterations were presented. The results of these analyses were estimated using both the list price and also where a confidential discount was incorporated. Only the results using the list price are presented here.

In the deterministic analysis of incremental cost per QALY (incremental cost-effectiveness ratio (ICER)), the ICER comparing idebenone with no treatment was €74,664. Idebenone was associated with 2.007 greater QALYs at a greater cost of €149,808. In the probabilistic analysis of incremental cost per QALY, the ICER comparing idebenone with no treatment was €74,738. Idebenone was associated with 2.005 greater QALYs at a greater cost of

€149,849. Using this analysis, and at a WTP threshold of €45,000, the probability of cost-effectiveness of idebenone, compared with no treatment, is 2.71%,

The RG requested several additional scenarios to be undertaken where patients' visual acuity relapses at varying time points, resulting in additional treatment. These additional scenarios increased the ICERs at varying rates, from €81,267 to €133,601 (probabilistic analysis). However, given the lack of long term data available and the lack of data on patients who have received additional courses of treatment with idebenone, the NCPE RG noted that it is not possible to assume that additional courses of treatment with idebenone will have the same effect on patients' eye sight compared with the original course of treatment, or that additional course of treatments would even be provided. Therefore the NCPE conducted an additional scenario where after 5 years, patients relapse and do not receive treatment, instead revert to the standard care arm's transition probabilities. This scenario was undertaken for all rates of relapse (0-100%). The results of this scenario analysis are presented below.

Figure 1: ICER-% relapses to standard care relationship



As the figure illustrates, as the proportion of patients that relapse and revert to standard care transition probabilities, the ICER increases significantly.

4. Budget impact of idebenone

Budget impact outputs at the list price and also at a confidential discount were estimated. Only the outputs at list price are presented here.

Idebenone is submitted for reimbursement under the High Tech Drugs Scheme. The proposed price to wholesaler of idebenone, per 180 tablets, is €6,173.42. The annual cost per patient per year is estimated to be €77,796 at list price.

Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €3 million. The NCPE RG amended the company's gross BI estimates for year 1-5, by making several amendments. Following these adjustments, the cumulative 5 year gross budget impact is estimated to be €3.7m at the list price. Idebenone is the first licensed treatment for LHON and currently patients do not receive pharmacological therapy. Therefore, there are no expected potential drug cost-offsets.

5. Patient submissions

A patient organisation submission of evidence was received from Fighting Blindness, during the course of this appraisal, and was included in full in the final report to the HSE.

6. Conclusion

The NCPE assessment of idebenone has demonstrated numerical improvements in visual acuity over placebo in one 24-week double-blind randomised placebo-controlled study. However the magnitude of this benefit in the long-term is uncertain and the most optimistic scenario is presented in the applicant's submission. There is a low probability of cost effectiveness and a high probability that the ICER exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that idebenone not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.