Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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idebenone (Raxone®) 150mg film-coated tablets SMC No. (1226/17)

Santhera Pharmaceuticals UK Ltd

07 April 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the ultra-orphan medicine process

idebenone (Raxone®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON).

SMC restriction: to patients with LHON who are not yet blind i.e. they do not meet the UK criteria to be registered as severely sight impaired.

In a 24-week double-masked randomised placebo-controlled study, patients who received idebenone had numerical improvements in visual acuity over placebo.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of idebenone. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON).[1]

Dosing Information

The recommended dose is 300mg three times daily. Tablets should be swallowed whole with water and not be broken or chewed. They should be administered with food as this increases the bioavailability of idebenone.

Treatment should be initiated and supervised by a physician with experience in LHON. There are no controlled clinical study data for treatment beyond six months.[1]

Product availability date

October 2015

Idebenone has been designated as an orphan medicine by the European Medicines Agency (EMA) and also meets SMC ultra-orphan criteria.

Background

Idebenone is a short chain benzoquinone with antioxidant properties. It is a synthetic analogue of co-enzyme Q10 but has the advantage of being able to cross the blood-brain barrier and reach the eye. Its postulated mechanisms of action are restoration of the generation of cellular energy, which is dysfunctional in patients with LHON, and neutralisation of oxygen free radicals in viable, but dormant, retinal ganglion cells. This rare, hereditary condition is caused by one of three main mutations in mitochondrial DNA and results in a sudden deterioration in vision. It is thought that idebenone may prevent or reverse vision loss depending on the time since symptom onset and the proportion of retinal ganglion cells already damaged.[2]

Idebenone has marketing authorisation for the treatment of visual impairment in patients with LHON. The submitting company has requested that SMC considers idebenone when positioned for use in a subgroup of the licensed indication, as a first line treatment for patients with LHON who are not yet blind, i.e. they do not meet the UK criteria to be registered as severely sight impaired.

Idebenone for use in the treatment of LHON has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

LHON causes sudden, painless, severe loss of visual acuity and colour vision, initially in one eye, but generally followed by vision loss in the second eye after two to four months. Data from 106 patients in the natural history population in a case record survey (CRS) found that the majority of eyes met the proxy criterion for legal blindness by one week after disease onset, more than 70% by three months and more than 80% by one year. LHON is a very rare condition caused by a mutation in mitochondrial DNA which disrupts the synthesis of ATP and produces free radicals, thus damaging retinal ganglion cells and ultimately destroying the optic nerve. The disease follows maternal inheritance and mothers with

the mutation pass it on to all of their children.[2] Approximately 50% of male and 10% of female carriers are affected by loss of vision and as some do not have a clear family history, they are unaware that they are carriers until vision loss occurs, at a median age of 24 years.[3, 4] Cigarette smoking is strongly correlated with sight loss and there is a weaker correlation with alcohol. Although LHON is usually irreversible, spontaneous recovery occurs in a proportion of patients and is more likely in patients with the T14484C and G3460A mutations.[2] Currently treatment is limited to best supportive care (BSC).

Idebenone is the first medicine to be licensed for LHON. Idebenone meets SMC ultra-orphan criteria. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely that no licensed treatments are available.

A patient and clinician engagement (PACE) meeting was held to consider the added value of idebenone in this patient group. In addition to the impact of the disease on the patients' vision, PACE participants highlighted that LHON can also have a deleterious effect on mental health, inducing clinical depression, social anxiety and suicidal thoughts. They noted that the lack of an approved treatment has led to many patients feeling hopeless and abandoned by the health service, and they reported that some patients stop having eye examinations as they see no point in the absence of effective treatment options.

Impact of new technology

Summary of evidence on comparative efficacy

The main evidence supporting the use of idebenone in LHON is from a phase II double-masked, randomised, placebo-controlled study, RHODOS, that recruited patients from 14 to 64 years of age with mitochondrial DNA mutations G3460A, G11778A or T14484C at >60% in blood and vision loss in at least one eye due to LHON (i.e. no other explanation for the visual loss) that had initially occurred within the previous five years.[2,3] A total of 85 patients were randomised, in a 2:1 ratio, to receive 24 weeks treatment with idebenone 300mg three times daily (n=55) or placebo (n=30), to be taken with meals. Randomisation was stratified by disease history (onset more versus less than one year prior to randomisation) and by type of mitochondrial DNA mutation.[2,3]

The primary outcome was best recovery from baseline at week 24 of visual acuity (VA), expressed as logarithm of the minimal angle of resolution (logMAR) values, in either right or left eye (whichever showed more improvement). If patients were able to see any letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, this was used to assess VA. In patients with no improvement in either eye, the value from the eye with least worsening was used. 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.[2] In the UK, people are generally certified as severely sight impaired (blind), if their best corrected vision (wearing appropriate glasses/contact lenses) is VA <3/60 (approximately logMAR 1.3), with a full visual field; or VA between 3/60 and 6/60 (logMAR 1.3 to 1.0) with a severe reduction of field of vision, such as tunnel vision; or VA ≥6/60 (logMAR 1.0) with a very reduced field of vision.[5] In RHODOS, logMAR ≥1.0 was used as a proxy for being legally blind.[2] 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.[2,3] The primary 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.[2,3]

The primary outcome of RHODOS was not achieved. There was a numerical improvement approximately equivalent to three ETDRS letters but no significant difference between treatment groups.[2] 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 (better seeing eye [BSE] at week 24 compared with BSE at baseline), or in change in VA of the eye that was better seeing at baseline.[3] When data from all 164 eyes were combined, there was a significant improvement in mean VA at 24 weeks for idebenone compared with placebo.[2,3] See Table 1 below.

Table 1: Primary and main secondary outcomes from RHODOS for the ITT population.[3]

	ITT Population	
	Idebenone N=53	**Placebo N=29**
Best recovery of logMAR VA in more improved eye at 24 weeks. (Primary outcome)	-0.135	-0.071
	Treatment difference -0.064 (95% CI: -0.184 to 0.055) p=0.291	
Mean change in best logMAR VA at 24 weeks (Key secondary outcome)	-0.035	0.085
	Treatment difference -0.120 (95% CI: -0.255 to 0.014) p=0.078	
Mean change in logMAR VA at 24 weeks of BSE at baseline	-0.030	0.098
	Treatment difference -0.128 (95% CI: -0.262 to 0.006) p=0.061	
Mean change in logMAR VA at 24 weeks for all 164 eyes	-0.054	0.046
	Treatment difference -0.100 (95% CI: -0.188 to -0.012) p=0.026	

ITT=intention to treat; logMAR= logarithm of the minimal angle of resolution; VA=visual acuity; N=number; CI=confidence interval; BSE=better seeing eye.

In a pre-specified analysis, deterioration to logMAR ≥1.0 in the subgroup of eight patients whose worse seeing eye (WSE) at baseline had a logMAR value ≤0.5 did not occur in any of the six patients receiving idebenone but did occur in both patients receiving placebo (p=0.036).[2]

A post hoc responder analysis assessed the proportion of patients in the ITT population with a clinically relevant recovery (CRR) of VA from baseline in at least one eye at 24 weeks. CRR was defined as either (i) improvement in VA from unable to read a single letter to able to read at least five letters on the ETDRS chart or (ii) improvement in VA by at least 10 letters on the ETDRS chart. A numerically, but not statistically significantly, higher proportion of patients receiving idebenone than placebo responded: 30% (16/53) versus 10% (3/29), respectively.[1, 2]

There was no significant difference between treatments in Health-Related Quality of Life assessed using the Visual Function (VF)-14 score in the 57 patients for whom data were available. The VF-14 is a validated method of assessing functional impairment in eye diseases by measuring the patient's ability to perform activities of daily living that depend on normal visual parameters.[6] There was also no significant difference between treatments in Clinical Global Impression of Change.[2]

A single follow-up visit study (RHODOS OFU) at a median of 30 months after the end of the 24-week RHODOS treatment period, included 58 patients (39 from the idebenone group and 19 from the placebo group).[2,7] Improvement in best VA over placebo (which did not reach statistical significance) was maintained although five patients reported taking idebenone in the intervening period; treatment difference from RHODOS baseline to RHODOS OFU was -0.173 (95% CI: -0.370 to 0.024, p=0.084).[2]

Supportive evidence was presented from an international expanded access programme (EAP) for LHON patients who were treated with idebenone and natural history data for untreated patients from a Case Record Survey (CRS).

In 2015 an analysis was conducted of 69 patients from the EAP who had onset of vision loss in the second eye less than 12 months before the baseline visit, one of the three main LHON mutations and post baseline efficacy data. The average age at baseline was 40 years and there were six children under 14 years. The proportions of patients with G11778A, G3460A and T14484C mutations were 59%, 18% and 16%, respectively. Mean time since onset was 7.2 months. All patients received idebenone, (generally 900mg daily) and mean treatment duration was 15.4 (range 2.8 to 36.2) months. The primary outcome of proportion of patients with CRR (defined as for RHODOS) in VA from nadir was achieved in 31% (19/62) patients and 24% (30/124) of eyes at the 6-month assessment and in 36% (17/47) of patients and 30% (28/94) of eyes at the 12-month assessment.[2] The proportion of patients with VA corresponding to the proposed positioning (<logMAR 1.0) was 31% (21/69).

An analysis of the CRS which provided natural history data for LHON patients in Europe/USA included data from 106 patients with one of the three main mitochondrial mutations, with known date of symptoms onset, who had been assessed ≤2 years after this and who had no recorded idebenone use (natural history population). The primary outcome was VA as a function of time since onset of symptoms. A total of 61% of eyes were already legally blind at presentation, of which 22% had reached "off-chart" VA. At nadir 96% of eyes were legally blind and 75% had reached "off-chart" VA. More than half of eyes deteriorated to logMAR ≥1.0 within one week of disease onset, increasing to over 70% within three months. By 12 months over 80% of patients' eyes were legally blind. In the 142 observations available for 12 to 24 months of onset, 78% of eyes remained legally blind. At the last available VA data point, mean 14.9 months after onset, 83% of the patients remained blind.[2]

Spontaneous CRR was assessed in 74 patients with data from at least one visit between three months and two years after presentation. The proportion of patients with logMAR <1.0 at baseline was 64% (47/74).[2] Overall, spontaneous CRR in VA from nadir was observed in at least one eye of 31% (23/74) of patients and in 24% (36/148) of eyes. The mean time from disease onset to spontaneous CRR was 9.9 months (range: 1.0 to 27.5 months). Analysis of spontaneous CRR in these 23 patients (using the better value from patients with two improved eyes) found a mean improvement of 39 letters (range: 5 to 90). Spontaneous CRR was more frequent in patients with the G3460A (50%, 6/12) and T14484C (43%, 3/7) than the G11778A mutation (26%, 14/55). Spontaneous CRR did not seem to depend on time since onset of symptoms (≤6 months=32% [20/63] or 6 to 12 months=33% [3/9]), although patient numbers were small. Of the 67 patients who could read letters on the chart at baseline, 79% (53/67) had clinically relevant worsening of VA post-presentation in at least one eye. Of the 47 patients who had VA logMAR <1.0 (not legally blind) at presentation, only 15% (n=7) retained this level of VA.[2]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Most patients in the RHODOS study reported at least one adverse event; (89% in the idebenone group and 87% in the placebo group) and these were considered to be treatment-related in five patients: one each of elevated blood triglycerides, left ventricular hypertrophy [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.[2] There were no treatment-related serious adverse events. One patient in each treatment group discontinued study medication due to adverse events.[3]

Most adverse events were mild or moderate in intensity and the most common adverse events for idebenone, versus placebo, were: nasopharyngitis (26% versus 17%), headache (24% versus 20%), influenza (11% versus 10%), elevated blood triglycerides (11% versus 10%) and cough (11% versus 0).

Other adverse events that were more common in the idebenone group compared with placebo were LVH (7.3% versus 0) and dizziness (5.5% versus 0).[2]

Idebenone may cause a reddish-brown discolouration of the urine which is harmless. However, care should be taken to ensure that other causes of urine discolouration are not masked by this effect. Idebenone tablets contain lactose and therefore should not be taken by patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. They also contain sunset yellow (E110) which may cause allergic reactions.[1]

Summary of clinical effectiveness issues

The pivotal RHODOS study did not meet the primary outcome and several secondary outcomes. Patients who received idebenone showed a numerical improvement over placebo for the primary outcome (best recovery of VA by week 24 in the most improved eye) which was approximately equivalent to three ETDRS letters.[3] The treatment effect seemed to be maintained 30 months after discontinuation of idebenone although some patients had taken idebenone in the intervening period.[7] There was also a numerical improvement for idebenone over placebo for the key secondary outcome of mean change from baseline to week 24 in best VA, which reached significance when data from all eyes were combined.[2,3] For most outcomes there was at least a trend towards a treatment benefit with idebenone.[2] In a very small subgroup (n=8) of patients whose WSE at baseline was logMAR ≤0.5, deterioration to logMAR ≥1.0 did not occur in any of the six patients receiving idebenone but did occur in both patients receiving placebo.[2] Overall in the study, improved vision did not translate to measurable improvement in quality of life.[3]

The submitting company has suggested that treatment duration would be between one and three years, however the Committee for Medicinal Products for Human Use (CHMP) of the EMA advised that there are uncertainties with respect to any benefit beyond six months treatment duration. A review of evidence across data sets found a higher proportion of patients/eyes with CRR in untreated patients after 36 months compared with treated patients after six months. The CHMP has recommended that long-term post-marketing data are collected.[2] Recovery of vision has been reported years after disease onset. The EMA noted that the benefit of early treatment has not been proven and did not restrict the marketing authorisation accordingly. However the European Public Assessment Report also noted that the overall tendency of improvement in vision in patients appeared to be mainly driven by patients with shorter disease history.[2]

RHODOS had a number of limitations. It was of short duration (24 weeks) and controlled data on longer-term outcomes are not available. The study population was very mixed, including patients in the acute stage and those with advanced disease progression, and with very different degrees of visual loss. The range of time since onset of vision loss was 2 to 62 months. This heterogeneity complicates interpretation of study results. There were several small subgroup and post hoc analyses.[3] The submitting company highlighted a limitation of the primary outcome which may bias results: if a patient had no improvement in either eye, the value used was the change from baseline in the eye with least worsening. However if the WSE was already “off-chart” and could not deteriorate any more, this value was considered as the least worsening value and this does not take into account any “less worsening” (retention of some vision) in the BSE.

Spontaneous recovery of vision is relatively common (observed in 31% of untreated patients in the CRS) and is a confounding factor. It may be masked in the idebenone-treated patients who accounted for two-thirds of the RHODOS study population. There is a risk that any spontaneous recovery occurring in patients receiving idebenone would be wrongly attributed to treatment benefit. The CHMP questioned the robustness of the study because the exclusion from the placebo group of a single patient, considered by the submitting company to be a natural history confounder, had a substantial effect on the results of some secondary outcomes; changing them from non-significant to significant.[2] A key limitation with respect to the proposed positioning is that only a small subgroup of 14% (12/85) of RHODOS study

patients reflected this positioning.[3] Post hoc subgroup analyses of these 12 patients found no significant difference between treatment groups for the primary or key secondary outcome. These results should be interpreted with caution due to small patient numbers. In the EAP and CRS, respectively, 30% (21/69) and 64% (47/74) of patients reflected the proposed positioning. Overall the CHMP was of the view that the data from the EAP and the CRS provided independent supportive evidence in favour of a treatment effect of idebenone.

Clinical experts consulted by SMC considered that idebenone is a therapeutic advancement as it may prevent or reverse vision loss in patients with LHON and is likely to be used in patients with early stage disease.

At the PACE meeting it was acknowledged that robust evidence for the efficacy of idebenone is limited and it is unlikely that another randomised controlled study versus placebo will be conducted. However they stressed that it is important that the reported benefit is not lost, as idebenone is the only safe option for LHON patients. The opportunity to access idebenone in Scotland, with the collection of efficacy and safety data in a drug registry, would increase the available evidence base. As the condition progresses to blindness very quickly after diagnosis, access to idebenone would offer potential benefits for only a short window but this may provide a therapeutic option for eligible patients until future treatment options become available.

Patient and clinical engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group and clinical specialist representation was held to consider the added value of idebenone, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- LHON is a rare genetic disorder that causes life-changing blindness without warning in young people. This is exceptionally debilitating and isolating, affecting education and career plans. Additionally LHON has a detrimental psychological impact on patients often inducing clinical depression. LHON can also cause practical, emotional and financial devastation for the whole family. There is a huge psychological impact on family members that carry the LHON genetic mutation as they live with the fear that they could also lose their sight at any time.

- Some LHON patients experience a degree of spontaneous improvement of visual acuity; however this is not usually complete. The PACE participants emphasised that the rate of spontaneous recovery that they have observed in their own clinical practice is much lower than the rate cited in the literature.

- A substantial proportion of patients feel that they have no choice but to self-medicate with nutritional supplements containing idebenone or co-enzyme Q10. These are not licensed medicines and there is a substantial safety risk due to potential inferior quality or counterfeit products, especially if purchased online.

- Idebenone is the only approved, treatment for LHON. It can improve the final visual outcome in a proportion of treated patients. Even partial reversal of visual loss would lessen the impact on education, career and ability to interact with vision-dependent media, thus reducing social isolation and significantly improving an individual's quality of life. The ability to access idebenone may also provide psychological benefit for relatives, both LHON carriers and non-carriers by relieving some of their fears for the future.

- PACE participants highlighted the challenges of obtaining robust evidence of the efficacy of idebenone in this rare disease. They noted that sufficient research has not been, and may never be, conducted to determine the real benefit of idebenone. They stressed that the reported benefit should not be dismissed, as these young patients have no safe alternative.

Additional patient and carer involvement

We received a patient group submission from the Leber's Hereditary Optic Neuropathy (LHON) Society, which is a registered charity. The LHON society has not received any pharmaceutical company funding in the past two years. A representative from the LHON Society participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Value for money

The submitting company presented a cost-utility analysis comparing idebenone with BSC to BSC alone for patients with LHON who are not yet blind (defined as logMAR <1.0). BSC was assumed to comprise of neuro-ophthalmologist visits, low vision rehabilitation and social care support.

A cohort Markov model was used to synthesise data and extrapolate costs and outcomes over a life-time (66 years) horizon. Health states in the model were defined based on ranges of VA on the logMAR scale for the BSE. The states used in the model were: logMAR <0.3, logMAR ≥0.3 and <0.6, logMAR ≥0.6 and <1.0, logMAR ≥1.0 and <1.3, logMAR ≥ 1.3 and <1.7, counting fingers, hand motion and light perception. Death was included as an absorbing state. The cycle length was three months and mid-cycle correction was applied. Discounting was applied to costs and benefits at 3.5% in the base case.

Three studies provided the clinical data supporting the economic submission. One randomised study, the RHODOS study), provided key short-term outcomes for both idebenone and BSC. Longer-term outcomes were taken from observational studies. These were a prospective EAP based study in idebenone treated patients and a retrospective CRS in untreated patients study. Data from these sources were used to estimate the various movements between health states within the model.

Transition probabilities were derived from the observed transitions over 3 month periods from each of three studies were as follows:

- Transitions for idebenone patients during months 0-3 and 3-6 were taken from RHODOS study data
- Transitions for idebenone patients during cycles from 6 to 36 months were taken from the EAP study
- Transitions for BSC patients during months 0-3 and 3-6 were taken from the RHODOS study placebo patient data
- Transitions for BSC patients during cycles from 6 to 36 months were taken from the CRS study

A total of 1536 transition probabilities were used in the model. Note that due to the very limited data in the three studies many transition probabilities were 0% or 100% due to frequencies of 0 or very small numbers (e.g. 1-3) in the observed data.

An important assumption was that patients remain in the same VA state they are in at the three year time point for the remainder of the model. This was justified in the submission by limited data available from 36 months and the expected natural history of the disease in which VA stabilises after a period of worsening.

Health benefits with idebenone were based on patients spending greater time in better VA health states with treatment than without treatment. VA state utility weights were applied to value the benefits of the

shift in VA state distribution in quality-adjusted life-years (QALYs). The utility weights were all taken from a single source.[9] This study included (n=325) patients with a variety of conditions who had visual impairment of 20/40 or worse in at least one eye. RHODOS quality-of-life data were available using disease specific measures. The submitting company stated that it was not possible to map these to the utility weight scale as no mapping algorithms exist for the scales in question therefore these data were not used. The submitting company also assumed that there were no important utility decrements for adverse events.

Resource use included medicine, monitoring visits and health and social care resource use related to blindness. Idebenone use was based on a dose of 900mg/day for a duration estimated from time-on-treatment data from the RHODOS and EAP studies. Median time-on-treatment was two years and it was assumed that after three years all patients would stop treatment. This assumption was justified by both observed data and expert consensus. Ophthalmologist visits were every three months in the first three years and annually thereafter for all patients, visit numbers was based on expert opinion.

Health care resource use resulting from blindness was included based on a previously published literature review.[10] The review was specifically related to patients with age-related macular degeneration. Given the lack of direct data on long-term resource use in LHON patients the quantities of resources used estimated in this review may be the most appropriate source. These estimates have been used extensively in other economic evaluations in which blindness was an important outcome.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of idebenone.

In the base case analysis, with the PAS, the reported incremental cost-effectiveness ratio (ICER) was £11,262 based on an incremental gain of 5.38 QALYs and incremental costs of £60,632. Reported scenario analysis included varying the discount rate, time horizon and sources of clinical effectiveness data. An analysis assuming a societal perspective was also conducted (i.e. including direct costs to patients and other services). Results of selected scenario analyses are shown in the table below:

Table 2 - Sensitivity analysis- with PAS

Scenario	ICER (£ per QALY)	Incremental costs (£)	Incremental QALYs
0% discount rate	Idebenone dominant (cheaper, more effective)	-5,180	10.46
6% discount rate	20, 293	73,560	3.62
30 year horizon	19,341	81,766	4.23
RHODOS data only	20,967	66,818	4.89
Societal perspective	Idebenone dominant	-240,392	5.38

One-way sensitivity analysis results indicated that the model was somewhat sensitive to the utility weight values and the time-on-treatment estimates for idebenone. Varying single utility weight values resulted in ICERs in the approximate range of £9,500 to £13,500. Varying the persistence on treatment parameter produced ICERs in the range of approximately £8,500 to £13,500.

An analysis of treatment effectiveness was reported upon request. This was conducted by increasing or decreasing the proportion of patients transitioning to worse VA states from all states in the model by

+/- 20% from the base case value. This was done separately for both idebenone and BSC groups holding the other group fixed at the base case values. At the lower and upper bounds for idebenone treatment effectiveness the ICER was £11,507 and £10,833. For BSC the lower and upper bounds of treatment effectiveness produced ICERs of £10,102 and £13,884.

The main weaknesses of the analysis were:

- As a result of the small number of observations there is a high degree of uncertainty regarding the base case estimates. Given the model structure it is possible that a single individual's observations may greatly influence the pattern of transition probabilities and therefore may greatly change the estimated QALY gains. Generally, if changing or removing a single individual's observations can greatly change the estimate of a population statistic (i.e. the true transition probability) the estimate should not be considered robust. There is a considerable probability that the base case may be a large overestimate or an underestimate of the true effect of treatment. Note that there is potential for larger overestimation in the base case because the base case treatment effect is close to a natural upper bound, almost all idebenone patients have relatively good outcomes (80% logMAR <0.3 at nine months) while almost no BSC patients have good outcomes (20% logMAR <0.3 at nine months). Due to the noted limitations of the clinical data available, the evidence for the magnitude of treatment effect used in the base case is weak.
- Sensitivity analysis around the transition probabilities (noted above) between VA states in the idebenone and BSC groups was limited and may not fully capture the uncertainty about treatment effectiveness. Firstly, varying the transition probabilities for idebenone and BSC separately may not accurately capture the uncertainty around the treatment effect as these parameters may be correlated. Secondly, varying the transition probabilities by 20% will have no effect on transition probabilities that were estimated at 0% in the base case. As previously noted, due to the very small number of observations and the large number of VA states there are a large number of 0% transition probabilities in the base case model. Uncertainty around treatment effectiveness is particularly important given the very small patient numbers informing the VA transition probabilities in the early model cycles and the importance of these estimates in determining the QALY gains from treatment. The company provided some additional sensitivity analysis to try and address the issue of the 0% transition probabilities in a more satisfactory way. In these analyses, for example, a 20% reduction in treatment effect resulted in 20% of patients assuming to transition to the next worse health state. This resulted in an ICER of £35,153 if the treatment effect of idebenone was assumed to 20% lower.
- The literature review of costs of blindness was 16 years old and focused on older patient group with a different condition (age-related macular degeneration). There are no costing studies available for LHON specifically. There is some concern that the estimated resource use and unit costs may not generalise well to LHON patients at the present time due to changing practice and differential inflation of health care costs. However, in the absence of more appropriate data these may be the best available estimates. Sensitivity analysis using a lower cost of blindness increased the ICER to £14,100.

*Other data were also assessed but remain commercially confidential.**

Impact beyond direct health benefits and on specialist services

AT the PACE meeting, attention was drawn to the fact that recovery of vision for some patients, even if only partial, would lessen the impact on education, career and mobility thus increasing independence and the likelihood to continue in previously chosen work. A partial increase in vision may also lessen the financial burden to the state associated with costs of providing health and social care services for patients with LHON

It was highlighted that the opportunity to access a safe licensed treatment option would also have a positive impact on the wider family both as concerned carers and LHON carriers.

Analysis provided by the submitting company suggests that idebenone may be associated with savings in societal costs including public sector payments (such as social security payments, housing benefit and council tax benefit) and reduced productivity losses to patients and unpaid carers.

Costs to the NHS and Personal Social Services

The submitting company estimated there would be three patients eligible for treatment with idebenone in year 1 reducing to two patients in year 5. The estimated uptake rate was 30% in year 1 (one patient) rising to 70% in year 5 (two patients).

*Other data were also assessed but remain commercially confidential.**

Conclusion

The Committee also considered the benefits of idebenone in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as idebenone is an ultra orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted idebenone for restricted use in NHS Scotland.

Additional information: comparators

There are no other treatments for LHON. Currently patients receive best supportive care.

Cost of relevant comparators

Drug	Dose Regimen	Cost (£)
Idebenone	300mg orally three times daily	38,608 (six months) 77,217 (one year) 231,650 (three years)

Cost of idebenone from Dictionary of medicines and devices accessed 19 December 2016. The Summary of product characteristics notes that controlled data are not available after six months treatment. The submitting company has suggested that treatment would last between one and three years.

References

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2. European Medicines Agency. CHMP Assessment Report. 2015.

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This assessment is based on data submitted by the applicant company up to and including 15 February 2017.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered

feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.