Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Raxone 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg idebenone.

Excipients with known effect: Each film-coated tablet contains 46 mg of lactose (as monohydrate) and 0.23 mg of sunset yellow (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange, round, biconvex film-coated tablet of 10 mm diameter, engraved with the Santhera logo on one side and "150" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Raxone is a licensed medicine which is currently indicated:

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

EAMS INDICATION (unlicensed):
Raxone is indicated:

- for slowing the decline of respiratory function in patients with Duchenne Muscular Dystrophy (DMD) from the age of 10 years who are currently not taking glucocorticoids. The decline of respiratory function must be confirmed by repeated measurements of pulmonary function prior to initiation of treatment (see section 5.1). Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not tolerated or is considered inadvisable (see section 4.4).

Footnote:
DMD patients who are receiving therapeutic doses of glucocorticoid for the treatment of DMD are not eligible to receive Raxone through EAMS; however, patients receiving no more than physiological doses of glucocorticoid as replacement therapy for adrenal suppression due to prior longstanding therapeutic doses of glucocorticoid, can be enrolled to receive Raxone through EAMS.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician with experience in DMD.

Posology

The recommended dose is 900 mg/day idebenone (300 mg, 3 times a day).

No data regarding a continuous treatment with idebenone beyond 12 months is available from controlled clinical trials with DMD patients.

Raxone is not currently approved for use in DMD patients taking concomitant glucocorticoids and should not be prescribed to such patients.

Special populations

Elderly

No specific dose adjustment is required for the treatment of DMD in elderly patients.

Hepatic or renal impairment

Patients with hepatic or renal impairment have not been investigated. Caution is advised in treatment of patients with hepatic or renal impairment (see section 4.4).

Paediatric population

The safety and efficacy of Raxone in DMD patients under 10 years of age have not yet been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on posology can be made.

Method of administration

Raxone film-coated tablets should be swallowed whole with water. Raxone should be administered with food because food increases the bioavailability of idebenone.

For patients unable to swallow a whole tablet, tablets may be crushed into semi-solid food. In patients being fed via a nasogastric tube or gastrostomy port, the tablets may be crushed into the liquid enteral feed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Monitoring

Patients should be regularly monitored according to local clinical practice.

Hepatic or renal impairment

No data are available in these populations. Therefore, caution should be exercised when prescribing Raxone to patients with hepatic or renal impairment.

Chromaturia

The metabolites of idebenone are coloured and may cause chromaturia, i.e. a reddish-brown discoloration of the urine. This effect is harmless, not associated with haematuria, and does not require any adaptation of dose or discontinuation of treatment. Caution should be exercised to ensure that the chromaturia does not mask changes of colour due to other reasons (e.g. renal or blood disorders).

Lactose

Raxone contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Raxone.

Sunset yellow

Raxone contains sunset yellow (E110) which may cause allergic reactions.

Use of glucocorticoids

Sufficient efficacy and safety data from clinical trials on the use of Raxone in patients with DMD taking glucocorticoids is lacking. Therefore Raxone cannot be recommended at this stage for use in DMD patients taking glucocorticoids and should not be prescribed to such patients as part of this EAMS.

Any decision to stop glucocorticoids should be separate from the decision to commence idebenone. To confirm that during this EAMS period these decisions are separate, a minimum period of three months without glucocorticoid therapy will be required unless there is specific clinical justification recorded on the Patient Enrolment Form explaining why glucocorticoids were stopped closer to the start of the EAMS (e.g specific significant side effects observed under glucocorticoid treatment).

Patients currently taking glucocorticoids may be considered for potential inclusion in the SIDEROS study.

4.5 Interaction with other medicinal products and other forms of interaction

Data from *in vitro* studies have demonstrated that idebenone and its metabolite QS10 do not exert systemic inhibition of cytochrome P450 isoforms CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 at clinically relevant concentrations of idebenone or QS10. In addition, no induction of CYP1A2, CYP2B6 or CYP3A4 was observed.

In vivo idebenone is a mild inhibitor of CYP3A4. Data from a drug-drug interaction study in 32 healthy volunteers indicate that on the first day of oral administration of 300 mg idebenone t.i.d., the metabolism of midazolam, a CYP3A4 substrate, was not modified when both drugs were administered together. After repeated administration C_{max} and AUC of midazolam were increased by 28% and 34%, respectively, when midazolam was administered in combination with 300 mg idebenone t.i.d. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving idebenone.

Idebenone may inhibit P-glycoprotein (p-gp) with possible exposure increases of e.g. dabigatran etexilate, digoxin or aliskiren. Idebenone is not a substrate for p-gp *in vitro*.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of idebenone in pregnant women has not been established. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Idebenone should only be administered to pregnant women or women of child-bearing age likely to become pregnant if it is considered that the benefit of the therapeutic effect outweighs any potential risk.

Breast-feeding

Studies in rats have shown that idebenone is excreted into maternal milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

There are no data concerning the effect of exposure to idebenone on human fertility.

4.7 Effects on ability to drive and use machines

Raxone has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions to idebenone are mild to moderate diarrhoea (usually not requiring the discontinuation of the treatment), nasopharyngitis, cough and back pain.

Tabulated list of adverse reactions

The following adverse reactions emerging from clinical trials in LHON patients, DMD patients or reported post-marketing in other indications are tabulated below. Frequency groupings are defined to the following convention: very common (≥1/10), common (≥1/100 to <1/10), not known (cannot be estimated from the available data).

System Organ Class	Preferred Term	Frequency
Infections and Infestations	Nasopharyngitis	Very common
	Bronchitis	Not known
Blood and lymphatic system disorders	Agranulocytosis, anaemia, leukocytopenia, thrombocytopenia, neutropenia	Not known
Metabolism and nutrition disorders	Blood cholesterol increased, blood triglycerides increased	Not known
Nervous system disorders	Seizure, delirium, hallucinations, agitation, dyskinesia, hyperkinesia, poriomania, dizziness, headache, restlessness, stupor	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Very common
Gastrointestinal disorders	Diarrhoea*	Common
	Nausea*, vomiting*, anorexia†, dyspepsia*	Not known
Hepatobiliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma- glutamyltransferase increased, blood bilirubin increased, hepatitis	Not known
Skin and subcutaneous tissue disorders	Rash†, pruritus†	Not known
Musculoskeletal and connective tissue disorders	Back pain	Common
	Pain in extremity*	Not known
Renal and urinary disorders	Azotaemia, chromaturia*	Not known
General disorders and administration site conditions	Malaise	Not known

*Adverse events for which it is currently assessed that there is sufficient data available to conclude a reasonable possibility for a causal relationship to Raxone
†Adverse events that medically cannot be excluded to potentially occur in case of lactose intolerance and hypersensitivity reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any adverse events by faxing or emailing the completed *EAMS safety reporting form*, as explained in the document *EAMS treatment protocol – Information on the pharmacovigilance system and requirements for reporting safety data.*

4.9 Overdose

No report of overdose has been received from the clinical studies. Doses up to 2250 mg/day have been administered in clinical studies showing a safety profile consistent with that reported in section 4.8.
There is no specific antidote for idebenone. When needed, supportive symptomatic treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, other psychostimulants and nootropics;
ATC code: N06BX13

Idebenone, a short-chain benzoquinone, is an anti-oxidant assumed to be capable of transferring electrons directly to complex III of the mitochondrial electron transport chain, thereby circumventing complex I and restoring cellular energy (ATP) generation under experimental conditions of complex I deficiency.

Duchenne muscular dystrophy (DMD)

Mechanism of action

In DMD, lack of dystrophin causes muscle cell membrane instability, uncontrolled influx of excessive Ca^{2+}-leading to intracellular Ca^{2+}-overload, production of cell-damaging reactive oxygen species, and mitochondrial complex I dysfunction and impaired ATP production. Under these circumstances, idebenone can enhance the transfer of electrons directly to complex III of the mitochondrial electron transport chain, thereby restoring cellular ATP generation and prevent the initiation of mitochondrial-driven muscle cell death. Idebenone also acts as a powerful antioxidant protecting muscle cells from exposure to reactive oxygen species.
In the mdx mouse model idebenone was shown to improve cardiac diastolic function and exercise performance.

Clinical safety and efficacy

The Phase III DELOS study

In DELOS, a total of 64 DMD patients not using glucocorticoids (discontinued glucocorticoid use >12 months prior to baseline or had never used glucocorticoids), 10-18 years of age, presenting with established respiratory function decline (i.e. PEF expressed as percent of predicted (PEF%p) <80%p) were randomised 1:1 to receive Raxone 900 mg/day (300 mg 3 times a day with food) (n=31) or placebo (n=33) for a period of 12 months (52 weeks).
The DELOS intent-to-treat (ITT) population had an average (SD) age of 14.3 (2.7) years, 92% of patients were non-ambulatory at baseline and 59% had an average Brooke score of 5 or higher. Average (SD) baseline values for pulmonary function outcomes in the ITT population were PEF%p: 53.8 (11.8) %p, FVC%p: 52.8 (18.1) %p, FEV1%p: 51.4 (18.5) %p, MIP%p: 41%p (19.6) %p, MEP%p: 26.6 (12.2) %p.
The primary endpoint was the 'change from baseline to week 52 in PEF%p', as assessed by spirometry during hospital visits and analysed with a mixed model for repeated measures. In the ITT population the between treatment group difference was 6.27%p for PEF%p (95%CI: 0.61%p-11.93%p; p=0.0306) and 28.09 L/min for the non-normalised PEF (95%CI: 2.69 L/min, 53.50 L/min; p=0.0308) (Table 1).

The outcomes for the primary and other respiratory function endpoints obtained by spirometry and calculated as percent of predicted or as non-normalised are shown in Table 1. In addition to the pre-specified analysis using a mixed model of repeated measures, post-hoc analyses using a random coefficient regression model with random slopes and intercepts (slope analysis) are also shown.

Table 1: DELOS: Outcomes for respiratory function endpoints from baseline to week 52

Endpoint (ITT population)	**Raxone (N=31)**	**Placebo (N=33)**
PEF%p		
Baseline mean (SD)	53.47 (10.26)	54.18 (13.16)
Change at Week 52*	-2.57 (-6.68, 1.54)	-8.84 (-12.73, -4.95)
	Estimated difference: 6.27 (0.61, 11.93); p=0.0306	
Slope analysis at Week 52**	-1.61 (-4.71, 1.48)	-7.42 (-10.43, -4.42)
	Estimated difference: 5.81 (1.62, 10.0); p=0.0070	
PEF (L/min)		
Baseline mean (SD)	217.7 (48.6)	233.8 (59.6)
Change at Week 52*	1.7 (-16.7, 20.1)	-26.4 (-43.8, -8.9)
	Estimated difference: 28.1 (2.7, 53.5); p=0.0308	
Slope analysis at Week 52**	-0.5 (-14.2, 13.1)	-23.6 (-36.8, -10.3)
	Estimated difference: 23.0 (4.5, 41.6); p=0.0154	
FVC%p		
Baseline mean (SD)	55.33 (15.82)	50.40 (19.99)
Change at Week 52*	-5.67 (-8.36, -2.99)	-8.95 (-11.47, -6.42)
	Estimated difference: 3.27 (-0.43, 6.97); p=0.0819	
Slope analysis at Week 52**	-2.55 (-4.38, -0.72)	-6.69 (-8.47, -4.90)

	Estimated difference: 4.13 (1.72, 6.54); p=0.0009		
FVC (mL)			
Baseline mean (SD)	1881 (465)	1862 (504)	
Change at Week 52*	-41 (-139, 56)	-175 (-267, -83)	
	Estimated difference: 134 (-0, 268); p=0.0503		
Slope analysis at Week 52**	-8 (-66, 49)	-131 (-187, -75)	
	Estimated difference: 122 (48, 197); p=0.0016		
FEV1%p			
Baseline mean (SD)	53.56 (16.07)	49.45 (20.59)	
Change at Week 52*	-4.23 (-8.21, -0.25)	-10.65 (-14.43, -6.87)	
	Estimated difference: 6.42 (0.92, 11.92); p=0.0230		
Slope analysis at Week 52**	-1.84 (-4.53, 0.85)	-8.71 (-11.33, -6.09)	
	Estimated difference: 6.87 (3.32, 10.41); p=0.0002		
FEV1 (mL)			
Baseline mean (SD)	1567 (382)	1596 (542)	
Change at Week 52*	12 (-118, 142)	-235 (-359, -111)	
	Estimated difference: 247 (67, 426); p=0.0079		
Slope analysis at Week 52**	13 (-70, 95)	-187 (-268, -106)	
	Estimated difference: 200 (91, 308); p=0.0004		

PEF = peak expiratory flow; FVC = forced vital capacity; FEV1 = forced expiratory volume 1s;
Analyses of hospital-based spirometry results. Data are least square means (95%CI).
*pre-specified analysis with Mixed Model for Repeated Measures
** post-hoc analysis using a random coefficient regression model with random slopes and intercepts.

No statistically significant differences between treatment groups were observed for the additional secondary endpoints of MIP%p, MEP%p and peak cough flow.

The results of pre-specified responder analyses showed a higher proportion of Raxone-treated patients who did not deteriorate in respiratory function tests between baseline and week 52 (Table 2).

Table 2: Responder rates in the ITT population for respiratory function test results

	Raxone (N=31)	**Placebo (N=33)**	**P value**
PEF%p	14 (45%)	8 (24%)	0.081
PEF (L/min)	18 (58%)	9 (27%)	0.013
FVC%p	7 (23%)	3 (9%)	0.141
FVC (mL)	15 (48%)	6 (18%)	0.011
FEV1%p	14 (45%)	4 (12%)	0.004
FEV1 (mL)	18 (58%)	11 (33%)	0.049

Data are the number and percentage of patients not deteriorating in respiratory outcome from baseline to week 52 (last observation carried forward). Data analysed by the Cochran-Mantel-Haenszel test.

Additional analyses on the effect of idebenone on bronchopulmonary adverse events (including airway infections reported as treatment emergent adverse events) indicated that the hazard ratio for the time to first bronchopulmonary adverse event was 0.327 (95% CI: 0.129, 0.830; p = 0.019) and 0.281 (95% CI: 0.123, 0.642; p = 0.003) for the total cumulative rate of events in favour of Raxone treatment.

As severe bronchopulmonary adverse events frequently require intervention with antibiotic treatment the number of patients using systemic antibiotics was analysed, as well as the duration of antibiotic use. Overall, seven patients (22.6%) reported eight periods of antibiotic use for the treatment of bronchopulmonary adverse events in the idebenone group compared to 13 patients (39.4%) reporting 17 periods of antibiotic use in the placebo group. The

cumulative duration of antibiotic use was 105 days among patients on placebo, which was longer compared to patients receiving idebenone (65 days).

Patients requiring assisted ventilation

There is no experience of initiating treatment with idebenone in DMD patients requiring assisted ventilation.

Paediatric population

In clinical trials in Friedreich's ataxia, 32 patients between the ages of 8 and 11 years and 91 patients between the ages of 12 and 17 years received idebenone at ≥ 900 mg/day for up to 42 months.

In the randomised, placebo-controlled RHODOS trial and the Early Access Programme in LHON, a total of 3 patients between the ages of 9 and 11 years and 27 patients between the ages of 12 and 17 years received idebenone at 900 mg/day for up to 33 months.

In the phase II study (DELPHI) in DMD, a total of 13 patients between the ages of 9 and 16 years received idebenone at 450 mg/day for up to 52 weeks. In the extension study to DELPHI, 7 patients between the age of 11 and 18 years were treated with 450 mg/day and 11 patients between the age of 12 and 18 years with 900 mg/day idebenone for up to 24 months.
In the DELOS trial in DMD, a total of 31 patients between the ages of 10 and 18 years received idebenone at 900 mg/day for up to 52 weeks.

This medicinal product was authorised for LHON under 'exceptional circumstances'.
This means that, due to the rarity of the disease, it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and the SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Food increases the bioavailability of idebenone by approximately 5- to 7-fold and therefore, Raxone should always be administered with food. The tablets should not be broken or chewed.

After oral administration of Raxone, idebenone is rapidly absorbed. On repeat dosing, maximum plasma concentrations of idebenone are reached on average within 1 hour (median 0.67 h range: 0.33-2.00 h). In phase I pharmacokinetic studies, proportional increases in plasma concentrations of idebenone were observed for doses from 150 mg to 1050 mg. Neither idebenone nor its metabolites showed time-dependent pharmacokinetics.

Distribution

Experimental data have shown that idebenone passes the blood-brain barrier and is distributed at significant concentrations in cerebral and muscle tissue. Following oral administration pharmacologically relevant concentrations of idebenone are detectable in the aqueous humour of the eye.

Biotransformation

Metabolism occurs by means of oxidative shortening of the side chain and by reduction of the quinone ring and conjugation to glucuronides and sulphates. Idebenone shows a high first pass metabolism resulting in conjugates of idebenone (glucuronides and sulphates (IDE-C)) and the phase I metabolites QS10, QS6, and QS4 as well as their

corresponding phase II metabolites (glucuronides and sulphates (QS10+QS10-C, QS6+QS6-C, QS4+QS4-C)). The main metabolites in plasma are IDE-C and QS4+QS4-C.

Elimination

Due to the high first-pass effect, the plasma concentrations of idebenone were generally only measurable up to 6 hours after oral administration of 750 mg Raxone, given either as a single oral dose or after repeated (14 days) t.i.d. dosing. The main route of elimination is metabolism, with the majority of dose excreted via the kidneys as metabolites. After a single or repeated oral dose of 750 mg Raxone, QS4+QS4-C were the most prominent idebenone-derived metabolites in urine, representing on average between 49.3% and 68.3% of the total administered dose. QS6+QS6-C represented 6.45% to 9.46%, whereas QS10+QS10-C and IDE+IDE-C were close to 1% or below.

Hepatic or renal impairment

No data are available in these populations.

Paediatric population

Whilst clinical trials experience in paediatrics with LHON is limited to patients of 14 years of age and above, pharmacokinetic data from population pharmacokinetic studies, which included paediatric Friedreich's ataxia and DMD patients of age 8 years and above, did not reveal any significant differences in the pharmacokinetics of idebenone.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Povidone K25
Magnesium stearate
Colloidal silica

Coating
Macrogol 3350
Poly(vinyl alcohol)
Talc
Titanium dioxide
Sunset yellow FCF (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White high-density polyethylene bottles with white polypropylene child-resistant tamper-evident twist-off caps containing 180 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC AND MARKETING AUTHORISATION HOLDER

Scientific Opinion Holder (for EAMS in DMD)
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8. SCIENTIFIC AND MARKETING AUTHORISATION NUMBER(S)

EAMS number (for DMD): 46555/0001
Marketing authorisation number (for LHON): EU/1/15/1020/001

9. DATE OF SCIENTIFIC OPINION AND AUTHORISATION

Date of scientific opinion (for EAMS): June 2017
Date of first authorisation (for LHON): 8 September 2015

Detailed information on this medicinal product is available on the website of the EMA
http://www.ema.europa.eu

Additional information:

Each prescribing physician will be provided with a ***EAMS physician pack*** containing all the relevant documents needed to manage patients receiving Raxone under EAMS.

As each patient signs the ***EAMS consent form***, they should be issued with an ***EAMS patient card***. This is a wallet-card sized and patients should be requested to carry it with them at all times. It alerts any other healthcare professional that may treat them, that the patient is receiving idebenone through an early access scheme, with details of their own DMD specialist service, out of hours contact details, and the company's contact details.

Contact information:

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