1. NAME OF THE MEDICINAL PRODUCT

Raxone Idebenone

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 FCF (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 Idebenone is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON) (see section 5.1).

4.2 Posology and method of administration

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

Posology

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

No data regarding a continuous treatment with idebenone beyond 6 months is available from controlled clinical trials.

Special populations

Elderly

No specific dose adjustment is required for the treatment of LHON 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 Idebenone** in LHON patients under 12 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 Idebenone film-coated tablets should be swallowed whole with water. The tablets should not be broken or chewed. **Raxone Idebenone** should be administered with food because food increases the bioavailability of idebenone.

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

Caution should be exercised when prescribing **Raxone Idebenone** to patients with hepatic or renal impairment. Adverse events have been reported in patients with hepatic impairment, which have resulted in temporary interruption or discontinuation of treatment

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

Sunset yellow

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

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 medicinal products 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. These medicines should be administered with caution in patients receiving idebenone. 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 potential likely to become pregnant if it is considered that the benefit of the therapeutic effect outweighs any potential risk.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of idebenone in milk (for details see 5.3). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from **Raxone idebenone** therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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 Idebenone 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 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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

No report of overdose has been received from the RHODOS, the LEROS and the PAROS studies. Doses up to 2,250 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

Mechanism of action

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. Similarly, in LHON idebenone can transfer electrons directly to complex III of the electron transport chain, thereby bypassing complex I which is affected by all three primary mtDNA mutations causing LHON, and restoring cellular ATP generation.

According to this biochemical mode of action, idebenone may re-activate viable-but-inactive retinal ganglion cells (RGCs) in LHON patients. Depending on the time since symptom onset and the proportion of RGCs already affected, idebenone can promote recovery of vision in patients who experience vision loss.

Clinical efficacy and safety

Clinical safety and efficacy of idebenone in LHON have been assessed in one double-blind, randomised, placebo-controlled study (RHODOS). Long term efficacy and safety have been studied in a post-approval open-label study (LEROS). Long term safety has been studied in a non-interventional post-authorisation safety study (PAROS).

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 received either 900 mg/day **Raxone Idebenone** or placebo for a period of 24 weeks (6 months). **Raxone Idebenone** was given as 3 doses of 300 mg daily, each with meals.

The primary endpoint “best recovery of visual acuity (VA)” was defined as the result from the eye experiencing the most positive improvement in VA from baseline to week 24 using 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 (Table 1).

Table 1: RHODOS: Best recovery of VA and change in best VA from baseline to week 24

Endpoint (ITT)	**Raxone Idebenone (N=53)**	**Placebo (N=29)**
Primary endpoint: Best recovery of VA (mean ± SE; 95%CI)	logMAR* –0.135 ± 0.041	logMAR –0.071 ± 0.053
	logMAR –0.064, 3 letters (–0.184; 0.055) p=0.291	
Main secondary endpoint: Change in best VA (mean ± SE; 95% CI)	logMAR –0.035 ± 0.046	logMAR 0.085 ± 0.060
	logMAR –0.120, 6 letters (–0.255; 0.014) p=0.078	

Analysis according to Mixed Model of Repeated Measures
One patient in the placebo group presented with ongoing spontaneous recovery of vision at baseline. Exclusion of this patient yielded similar results as in the ITT population; as could be expected, the difference between idebenone and placebo arm was slightly larger.
*logMAR - **Log**arithm of the **M**inimum **A**ngle of **R**esolution

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 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.

In a single-visit observational follow-up study of RHODOS VA assessments from 58 patients obtained on average 131 weeks after discontinuation of treatment indicates that the effect of **Raxone Idebenone** may be maintained.

A post-hoc responder analysis was performed in RHODOS evaluating the proportion of patients who had a clinically relevant recovery 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 **Raxone Idebenone** in an Expanded Access Programme (EAP) and from 94 untreated patients in a Case Record Survey (CRS).

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

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

In 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.

In LEROS; a total of 199 LHON patients were enrolled in this open – label study. Over half (112 [56.6%]) had the G11778A mutation, whereas 34 (17.2%) had the T14484C mutation and 35 (17.7%) had the G3460A mutation. The mean age at Baseline (BL) was 34.2 years. Patients received 900 mg/day **Raxone Idebenone** for a period of 24 months. **Raxone Idebenone** was given as 3 doses of 300 mg daily, each with meals.

The primary endpoint in LEROS was the proportion of eyes that achieved a Clinically Relevant Benefit (CRB) (that is, in which there was either a Clinically Relevant Recovery [CRR] of VA from Baseline or a Clinically Relevant Stabilization [CRS]) at Month 12 in those patients that started treatment with **Raxone Idebenone** ≤1 year after the onset of symptoms, compared to eyes of patients from an external Natural History (NH) control group. CRB was observed in 42.3% of eyes from LEROS patients, in contrast to 20.7% eyes from NH patients. Clinically, this represents a relevant 104% relative improvement compared to spontaneous CRB that may occur in the control NH eyes. The estimated difference between treatment and control was statistically significant (p-value 0.0020) in favor of **Raxone Idebenone** presenting an Odds Ratio (OR) of 2.286 (95% confidence limits 1.352, 3.884).

One of the secondary endpoints in LEROS was the proportion of eyes with CRB in patients treated with **Raxone Idebenone** >1 year after the onset of symptoms, with CRR of VA from Baseline or CRS in which Baseline VA better than 1.0 logMAR was maintained at Month 12 compared to an external NH control group. CRB was observed in 50.3% eyes of LEROS patients and 38.6% eyes of NH patients. The difference between the two groups was statistically

significant in favor of **Raxone Idebenone** presenting a p-value of 0.0087 and OR [95% CI] of 1.925 [1.179, 3.173].

A total of 198 patients received treatment with **Raxone Idebenone** and were included in the Safety Population. The mean duration of treatment in the Safety Population was 589.17 days (range: 1 – 806 days), which was equivalent to a total exposure of 319.39 person-years. A total of 154 (77.8%) of the patients undertook treatment for >12 months. A total of 149 (75.3%) patients underwent treatment at the >18-month timeframe; at the >24-month timeframe, this was 106 (53.5%). A total of 154 (77.8%) patients reported Treatment Emergent Adverse Events. The Adverse Events (AE) reported were mainly of mild or moderate severity; 13 (6.6%) patients who received **Raxone Idebenone** treatment reported severe AEs. Forty-nine (24.7%) patients reported AEs that were considered by the Investigator to be treatment-related. Twenty-seven (13,6%) patients experienced Serious Adverse Events and ten (5.1%) had AEs that led to permanent discontinuation of study treatment. No new safety concerns have emerged in patients with LHON enrolled in the LEROS study.

PAROS was a post-authorization non-interventional safety study designed to collect longitudinal safety and effectiveness data in routine clinical settings in patients prescribed with **Raxone Idebenone** for the treatment of LHON. This study was conducted at 26 centres in 6 European countries (Austria, France, Germany, Greece, Italy and The Netherlands).
In the long-term safety study PAROS, a total of 224 LHON patients with a median age of 32.2 years at baseline received treatments with **Raxone Idebenone** and were included in the Safety population. Over half of the patients (52.2%) had the G11778A mutation; 17.9% had the T14484C mutation, 14.3% had the G3460A mutation, and 12.1% had other mutations. Time in treatment of these patients is displayed in the table 3 below.

Table 3: Time in treatment (Safety Population)

Time in treatment	**Idebenone-naïve at baseline**	**Idebenone non-naïve at baseline**	**All**
N	39	185	224
Day 1	39 (100.0%)	185 (100.0%)	224 (100.0%)
≥ 6 months	35 (89.7%)	173 (93.5%)	208 (92.9%)
≥ 12 months	30 (76.9%)	156 (84.3%)	186 (83.0%)
≥ 18 months	20 (51.3%)	118 (63.8%)	138 (61.6%)
≥ 24 months	14 (35.9%)	93 (50.3%)	107 (47.8%)
≥ 30 months	8 (20.5%)	68 (36.8%)	76 (33.9%)
≥ 36 months	8 (20.5%)	54 (29.2%)	62 (27.7%)

The mean duration of exposure is of 765.4 days (SD 432.6 days)

The long-term safety profile of **Raxone Idebenone** in the treatment of patients with LHON was evaluated when used under conditions of routine clinical care.

A total of 130 patients (58.0% of the Safety population) reported 382 Treatment Emergent Adverse Events (TEAEs). Eleven (4.9%) patients reported severe Adverse Events (AEs). Fifty (22.3%) patients reported 82 TEAEs that were considered by the Investigator to be drug-related. Thirty-four (15.2%) patients had 39 TEAEs that led to discontinuation of **Raxone Idebenone** treatment. Twenty-five (11.2%) patients experienced 31 serious TEAEs.

There was one death in the study, in an 81-year-old male patient who died of terminal prostate carcinoma, which was assessed by the Investigator as unrelated to **Raxone Idebenone**.
No new safety concerns have been identified with long-term treatment with **Raxone Idebenone** in patients with LHON when used under conditions of routine clinical care in the PAROS study. The safety profile of **Raxone Idebenone** observed in PAROS was similar to that from a previous open-label study (the LEROS study).

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 RHODOS and the EAP 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 PAROS, only nine patients under 14 years of age were included and received **Raxone Idebenone** at 900 mg/day.

5.2 Pharmacokinetic properties

Absorption

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

After oral administration of **Raxone Idebenone**, 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).

Distribution

Experimental data have shown that idebenone passes the blood-brain barrier and is distributed at significant concentrations in cerebral tissue. Following oral administration pharmacologically relevant concentrations of idebenone are detectable in the aqueous humor 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 Idebenone**, 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 Idebenone**, 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 represented 6.45% to 9.46%, whereas QS10+QS10-C and IDE+IDE-C were close to 1% or below.

Linearity/non-linearity
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.

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 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

Tablet core

Cellulose, microcrystalline
Lactose monohydrate
Croscarmellose sodium
Povidone (K25)

Silica, colloidal anhydrous
Magnesium stearate

Film-coating
Poly(vinyl alcohol)
Macrogol 3350 (polyethylene glycol)

Titanium dioxide (E 171, CI 77891)
Talc
Sunset yellow FCF (E 110, CI 15985) aluminum lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30°C
After opening, the product can be used until the expiry date as detailed on the box.

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. MANUFACTURER

Santhera Pharmaceuticals Switzerland AG
HOHENRAINSTRASSE 24, CH-4133
PRATTELN, SWITZERLAND

8. MARKETING AUTHORISATION HOLDER

Megapharm LTD,
HATIDHAR ST. 15, RA'ANANA, ISRAEL

9. MARKETING AUTHORISATION NUMBER(S)

159-18-34904

10. Revised in September 2023 according to MOHs guidelines .

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