swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Raxone

International non-proprietary name: idebenone
Pharmaceutical form: film-coated tablets
Dosage strength(s): 150 mg
Route(s) of administration: oral
Marketing authorisation holder: Chiesi SA
Marketing authorisation no.: 68063
Decision and decision date: approved on 1 March 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CPK	Creatine phosphokinase
CRB	Clinically relevant benefit
CRR	Clinically relevant recovery
CRS	Case record survey
CRS	Clinically relevant stabilisation
CRW	Clinically relevant worsening
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EAP	Expanded Access Program
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Environmental risk assessment
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
gGT	Gamma-glutamyltransferase
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LHON	Leber's Hereditary Optic Neuropathy
logMAR	Logarithm of the Minimum Angle of Resolution
LoQ	List of Questions
LVH	Left ventricular hypertrophy
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
Max	Maximum
MCV	Mean corpuscular volume
MELAS	Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes
Min	Minimum

mITT	Modified Intention to Treat
MRHD	Maximum recommended human dose
mtDNA	Mitochondrial DNA
N/A	Not applicable
NH	Natural history
NO(A)EL	No observed (adverse) effect level
OFU	Open follow-up
OR	Odd's ratio
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PT	Preferred term
RGC	Retinal ganglion cells
RMP	Risk management plan
RNFL	Retinal nerve fibre layer
ROS	Reactive oxygen species
SAE	Serious adverse event
sCRR	Spontaneous clinically relevant recovery
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
t.i.d.	Three times a day
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
ULN	Upper Limit of Normal
UV	Ultraviolet spectrometry
VA	Visual Acuity
WBC	White Blood Cell

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for idebenone in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 26 October 2021.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

Raxone is indicated for the treatment of visual impairment in adolescent patients from 12 years of age and adult patients with Leber's Hereditary Optic Neuropathy (LHON) (see section "Properties/Effects")

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose is 900 mg/day idebenone (300 mg, 3 times a day).
No data regarding continuous treatment with idebenone beyond 6 months are available from controlled clinical trials.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	18 October 2021
Formal objection	1 November 2022
Response to formal objection	15 November 2021
Formal control completed	1 December 2021
List of Questions (LoQ)	24 February 2022
Response to LoQ	6 July 2022
Preliminary decision	5 October 2022
Response to preliminary decision	5 December 2022
Labelling corrections	2 March 2023
Response to labelling corrections	13 April 2023
2nd labelling corrections	6 July 2023
Response to 2nd labelling corrections	27 July 2023
3rd labelling corrections	1 November 2023

Response to 3rd labelling corrections	1 December 2023
Final decision	1 March 2024
Decision	approval

3 Medical context

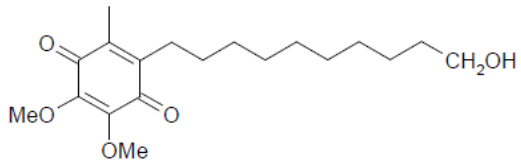
Leber's Hereditary Optic Neuropathy (LHON) is a rare mitochondrial disease resulting from mutations in the mitochondrial (and rarely nuclear) genome. LHON is characterised by a (sub)acute onset, painless progressive loss of central vision with cecocentral scotoma, and loss of colour vision. Overall, prognosis is poor, with the majority of patients experiencing visual loss of more than 90%.
LHON mainly affects male adolescents and young adults, but late onset disease has also been reported. In Europe, the prevalence of LHON is 0.5 to 1 per 50,000 inhabitants (Man et al. 2002, Leo-Kottler & Wissinger, 2011, Poincenot et al., 2020).
The most frequent mutations correspond to point mutations in the mitochondrial DNA (mtDNA). Located at nucleotide positions 11778 (70% of cases in Northern Europe, 90% of Asian cases), 3460 (8-25% of cases) and 14484 (10-15% of cases overall, 86% of LHON cases in Quebec, Canada), these most frequent LHON mutations lead to the impairment of distinct complex I subunits, resulting in mitochondrial dysfunction with reduced ATP synthesis, increased generation of reactive oxygen species (ROS), and redox intolerance. These most frequent LHON mtDNA mutations differ with respect to their frequency, penetrance, sex distribution, severity of visual loss, as well as their clinical prognosis (probability of visual recovery). Due to their intense energy metabolism, retinal ganglion cells (RGCs) are specifically vulnerable to any oxidative stress due to their high energy requirements and unique anatomical characteristics. If mitochondrial function is not restored, the cells will undergo apoptosis, resulting in permanent loss of function. Impaired RGCs remain viable up to 5 years after onset. However, due to its ubiquitous expression, extraocular manifestations including cardiomyopathy, cardiac arrhythmias (Wolff-Parkinson-White syndrome), diabetes, or neurological symptoms may complicate the clinical syndrome. Correspondingly, overlap syndromes of LHON and MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes), another mitochondrial disease, have been reported.

Therapeutic objectives refer to the prevention of Visual Acuity (VA) decline and the recovery of impaired VA. So far, no substance has been licensed for the therapy of LHON in Switzerland. Regarding the established negative influence of alcohol consumption and smoking on LHON as manifesting factors, patients are recommended not to smoke or drink.
Idebenone, a short-chain benzoquinone and coenzyme Q10 analogue, is thought to by-pass the complex I deficiency in LHON, with no respect to the underlying mutation, improve mitochondrial energy metabolism, reduce oxidative stress, and inhibit lipid peroxidation. Due to the mechanism of action, usage is not limited to a specific mutation.

4 Quality aspects

4.1 Drug substance

INN: Idebenone
Chemical name: 2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methyl-cyclohexa-2,5-diene-1,4-dione
Molecular formula: $C_{19}H_{30}O_5$
Molecular mass: 338.44 g/mol
Molecular structure:



Idebenone is a yellow-orange crystalline powder. Idebenone is practically insoluble in aqueous media.

The drug substance is manufactured by a multiple step chemical synthesis followed by crystallisation. The synthesis of the drug substance and the necessary in-process controls are described in detail.

The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent quality of idebenone.

Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Raxone film-coated tablets 150 mg are orange, round, biconvex film-coated tablets, debossed with the Santhera logo on one side and ‘150’ on the other side.

Raxone film-coated tablet manufacture involves standard unit operations, mixing, wet granulation, drying, screening, blending, compression, and film coating.

For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include the parameters of appearance, identity (HPLC, UV), assay (HPLC), uniformity of dosage units, degradation products (HPLC), dissolution, and microbial tests. Analytical methods have been described and validated according to ICH requirements.

Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Raxone (idebenone), the Nonclinical Assessment Division conducted an abridged evaluation based on the EMA assessment report (Procedure No. EMEA/H/C/003834, dated 25.06.2015) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Raxone in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised, and all nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There is no safety concern regarding impurities and excipients.

According to the ERA provided by the applicant, the risk of idebenone to the environment is assumed to be low.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data in this application has been carried out in reliance on the previous regulatory decision by the EMA. The available assessment report and corresponding product information from EMA were used as a basis for the clinical pharmacology evaluation.

6.2 Dose finding and dose recommendation

No dose studies have been performed. Reports from published studies on LHON refer to doses ranging from 180 to 675 mg/day (Carelli et al., 2011, Mashima et al., 2000). Animal studies theoretically suggest that 300 mg 3 times a day (t.i.d.) may give aqueous humour levels in humans in the range where idebenone prevented ganglion cell death in non-clinical models. Additional data obtained in patients with Friedreich's Ataxia (FA) showed that the dose of 2250 mg/day provided no additional benefit over 900mg/day.

In the light of the available data, the applicant proposed that a dose of 900 mg/day would be likely to be both well tolerated and adequate for efficacy testing and hence selected this dose to be administered as 3 equally divided doses t.i.d. for the pivotal Phase 2 trial.

6.3 Efficacy

The clinical study program for LHON comprises the following efficacy studies:

SNT-II-003 (RHODOS). RHODOS was a double-blind, randomised, placebo-controlled study. Its primary objective was to determine whether the administration of idebenone in LHON subjects with onset within the last 3 months mitigates visual loss in the initially least affected eye. A second confirmatory controlled study had originally been planned, but later considered as not feasible due to the orphan character of LHON. This was reflected by the difficulties to recruit sufficient numbers of newly diagnosed subjects eligible for RHODOS. The study protocol therefore had to be amended with respect to the inclusion of subjects with a disease duration of up to 5 years and the primary objective to determine whether idebenone can improve visual function in LHON subjects.

SNT-II-003-OFU: RHODOS-FU. This single-visit Observational Follow-Up study enrolling previous participants in RHODOS aimed to ascertain the post-study (off-treatment) durability of any benefit in VA obtained during RHODOS.

SNT-IV-005: LEROS. LEROS was an Open-Label Study to assess the efficacy and safety of Raxone® in LHON patients. At Swissmedic's request, the applicant provided the final clinical study report (CSR). The study was completed on 31 August 2021, and the final CSR was launched on 13 October 2021. LEROS was conducted in Europe and the US.

SNT-EAP-001: This **Expanded Access Program (EAP)** was established in November 2011 to provide Raxone for the treatment of individual ‘named LHON patients’ corresponding to this product exposure registry proposed by EMA as a post-authorisation follow-up measure. Responder analyses of VA outcomes and safety data of 61 participants of the EAP were included for additional evidence of efficacy (SNT-EAP-001).

SNT-IR-006: Case Record Survey (CRS). To address the 2011 marketing authorisation application (MAA) proposition, a case record survey (CRS) of the natural history of LHON from 383 individual LHON patients was established. The results were also included in the 2014 MAA. As 49% of subjects reported idebenone use, VA outcomes for these patients have been compared to the outcomes of untreated patients.

6.3.1 Pivotal studies

6.3.1.1 RHODOS

Study design. RHODOS was a randomised, placebo-controlled, double-blind parallel group study with treatment duration of 24-weeks (verum:placebo 2:1).

Study dose. Daily dose 900 mg (300 mg t.i.d. with food).

Study groups. Randomisation was stratified by LHON mutation subtype and by history of disease duration (≤1 year or >1 year prior to enrolment).

Efficacy measures. Primary and main secondary endpoints, as well as other secondary endpoints including responder analyses, were based on the assessment of visual acuity (VA). Other ophthalmic efficacy measures included assessments of colour contrast sensitivity and visual fields. Retinal nerve fibre layer (RNFL) thickness was also measured as an anatomical outcome, changes in which are associated with disease progression in LHON.

As most eyes in the chronic stage have already reached VA nadir (maximum worsening), the therapeutic objectives were (1) recovery reflected by the Clinically Relevant Recovery (CRR) and (2) prevention of further deterioration reflected by Clinically Relevant Worsening (CRW) at any VA level on-chart, or Clinically Relevant Stabilisation (CRS) if VA is still better than legally blind.

Statistical analysis. RHODOS was prospectively powered assuming a VA change of logMAR (Logarithm of the Minimum Angle of Resolution) -0.05 ± 0.3 in the placebo group and logMAR – 0.25 ± 0.3 in the Raxone® group. Such a difference (equivalent of 10 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart) was considered relevant from a clinical point of view. 84 patients would provide 80% statistical power to reject the null hypothesis of no difference in VA change between both groups. Separate analyses of the primary and selected secondary endpoints were pre-specified for subgroups such as mutation type, history of disease onset, and smoking status.

Primary efficacy endpoint. Best recovery of logMAR VA (defined as the result from the eye experiencing the most positive improvement in VA using ETDRS charts) between Baseline and Week 24 in either the right or left eye (‘Best Recovery of VA’).

Main secondary efficacy endpoint: Change of best VA at Week 24 (defined as the difference between best VA in either the left or right eye) compared to the best VA at Baseline (best eye at Baseline) (‘Change in Best VA’).

Study populations. Safety Population. 85 patients aged ≥ 14 years, randomised and treated (55 patients with Raxone® and 30 patients with placebo). **Modified ITT population (mITT).** 81 subjects (53 patients treated with Raxone® and 28 patients treated with placebo).

Demographics. Both groups were matched for demographic characteristics such as age at baseline, gender, genotype, and time since onset at baseline.

RHODOS efficacy results

For the **primary endpoint, *best recovery in VA***, there was **only a trend**, but no statistically significant difference between both arms after 24 weeks (Estimated difference ± SEM: -0.100 ± 0.058 (95% CI -0.214, 0.014), [5 letters], p-value 0.0862).

For the **main secondary endpoint, *change in best VA***, there was a statistically significant difference: while there was a worsening between baseline and Week 24 for patients on placebo, Raxone®-treated subjects showed a small improvement in best VA (Estimated difference ± SEM: -0.160 ± 0.065 (95% CI -0.289, -0.031), [8 letters], p-value 0.015)

For further secondary VA endpoints, there were also statistically significant differences in the mITT population in favour of Raxone®: The effect for the *change in VA followed for the patients’ best eye at Baseline to Week 24* was logMAR -0.165 (8 letters, p-value 0.0126) and the *change in VA for all eyes from Baseline to Week 24* was logMAR -0.138 (6 letters, p-value 0.0014).

6.3.1.2 LEROS (SNT-IV-005) (External natural history controlled, open-label intervention study to assess the efficacy and safety of long-term treatment with Raxone® in Leber's hereditary optic neuropathy (LHON))

The CHMP had requested specific obligations to complete post-authorisation measures for the marketing authorisation (MA) under exceptional circumstances of Raxone®, including an external natural history controlled, open-label intervention study to assess the efficacy and safety of Raxone® in the treatment of LHON patients, including long-term treatment. To address this obligation, LEROS was performed as a multi-centre interventional open-label study to assess the efficacy in the promotion of recovery or stabilisation of visual acuity (VA) and safety of Raxone® in idebenone-naïve LHON Patients.

The final CSR is dated 8 October 2021. Upon Swissmedic's request, the applicant provided the final CSR for LEROS (SNT-IV-005), finalised on 31 August 2021. Recruitment was completed on 9 March 2019, the final CSR was launched on 13 October 2021.

Study medication. Raxone® 150 mg film-coated tablets at a daily dose of 900 mg/day (2 x 150 mg to be taken orally 3 times daily with meals.

Study duration. 24 months

Study design. Patients aged ≥12 years were subdivided into 2 groups according to LHON onset (subacute population with an onset in the second eye ≤ 1 year, chronic population with an onset in the second year > 1 year).

Study amendments. The sample size was recalculated after database lock and data cleaning from the SNT-CRS-002 study (recalculated number of patients: 2x80). The LEROS study protocol was then amended (Amendment #2 dated 6 March 2019) to update the number of patients to be enrolled for the primary analysis.

Inclusion criteria. Patients with a diagnosis of LHON and no other explanation for visual loss, aged ≥12 years and with onset of symptoms within ≤5 years prior to Baseline.

Exclusion criteria. Known history of clinically significant lab elevations (> 3 x Upper Limit of Normal (ULN) of AST, ALT or creatinine).

Study population. 199 patients (198 treated) were enrolled at 29 sites across 10 countries in the EU and US after extension of the recruitment period due to the orphan character of LHON. Confirmation of genetic mutation was not a requirement for inclusion in the study at baseline, but rather at visit 4. Therefore, 15 subjects were later diagnosed with other than the 3 main LHON mtDNA mutations G11778A, G3460A, and T14484C. For ethical reasons, patients already on treatment were allowed to continue on Raxone®. Their data were included in the safety analysis and in some of the non-comparative analyses.

The **ITT population** (N=196) consisted of all patients enrolled in LEROS who provided at least 1 post-Baseline VA assessment. It was subdivided into 2 cohorts according to the onset of symptoms (subacute cohort with symptom onset in the most recent eye ≤1 year at Baseline and chronic cohort with symptom onset in the most recent eye >1 year at Baseline) served to evaluate the efficacy endpoints where no comparisons were made between LEROS patients and natural history (NH) patients.

Patients with a genotype corresponding to 1 of the 3 main mtDNA mutations G11778A, G3460A, or T14484C, and treated with at least 1 dose of the study medication and at least 1 post-Baseline VA assessment, were enrolled in the mITT population (181 patients, 99 subacute, and 82 chronic patients), which served to evaluate exclusively the efficacy endpoints where a comparison was made between LEROS patients and NH patients. The **safety population** included 198 subjects.

An **External Natural History (NH) control set** was derived from 2 case record surveys: SNT-IR-006 (CRS-1) collected historically documented VA data from patients with a genetically confirmed diagnosis of LHON. There were no exclusion criteria applied, and patients were not required to attend clinic visits for this survey. SNT-CRS-002 (CRS-2) collected data from all patients of the participating sites who fulfilled specific, prospectively defined, inclusion criteria. In order to ensure comparability between the LEROS population and those in the NH control set, the subjects from CRS-1 and CRS-2 were selected based on the LEROS inclusion/exclusion criteria and the criteria for inclusion in the LEROS mITT population: carriers of only 1 of the 3 major LHON mtDNA mutations, age ≥ 12 years, no other cause of visual impairment apart from LHON, defined date of symptom onset (at least known month and year), onset of symptoms ≤ 5 years at the Baseline visit, and at least 2 VA assessments of defined dates (at least known month and year). Overall, 372 patients with 731 eyes were included in the NH comparator group.

In order to optimise the comparability of patient data from the NH control set and the LEROS ITT population, a matching algorithm was established in the study protocol for the primary and secondary endpoints. These subsets were matched separately for all the efficacy analyses using the matching rules defined in the study protocol. A total of 8 datasets were generated according to the time since the onset of symptoms (Months 6, 12, 18, and 24 for time since symptom onset ≤ and > 1 year) at Baseline and the follow-up time.

Matching algorithm for the primary endpoint considered. Any eye with a VA observation at any time point in the NH control set which had a follow-up VA assessment within 12 ± 3 months was retained for use as a possible Baseline observation. For each eye in the NH control subset, the VA observation for which time since onset of symptoms was closest to the average time since onset of symptoms at Baseline calculated for LEROS was selected as the Baseline VA observation for that eye. Any eye in the NH control subset with a Baseline VA observation >6 months after the average time since onset of symptoms at Baseline in LEROS was discarded. This “final NH control subset” was used for the primary endpoint. This approach aimed to closely match Baseline observations in the final NH control subset to the Baseline in the LEROS ITT population.

Matching algorithm for the secondary endpoints. All available eyes in the external NH control set were considered, regardless of whether the eye in question was used in the control group for the primary objective or not.

Exposure. By month 12, 47 out of 198 treated patients had discontinued the study drug, by month 24 this number had increased to 57 patients.

Demographics and other baseline characteristics. The majority of patients were male **(**mITT 144/196 subjects (73.5%)). Onset in the second eye was ≤1 year in 109 subjects and > 1 year in 87 subjects. Genotype was G11778A in 57.1% of the mITT population, G3460A in 17.9%, and T14484C in 17.3%. Mean age at baseline was 34.1 years (SD 15.2, range 12.1 to 79.2 years).

Regarding the comparison of LEROS matched mITT and NH matched comparator, both groups were well-balanced for age at baseline and age at first symptom onset. It is to note that the NH matched comparator group included a higher percentage of males (83% vs. 68.8%) and G11778A genotype carriers (72.6% vs. 50.0%), and a lower proportion of T14484C genotype carriers (11.3% vs. 27.5%) compared to the LEROS matched mITT.

Study visits were scheduled at Month 1, Month 3, Month 6, Month 9, Month 12, Month 18, and Month 24. Visit 8 (Month 24) was the endpoint of treatment. Visit 9 was a follow-up, 28-35 days after study medication discontinuation.

Study assessments. Visual Acuity (VA) in LEROS patients was evaluated by means of the ETDRS (Early Treatment Diabetic Retinopathy Study [ETDRS]) chart, following standardised procedures upon each study visit. VA values were recorded in logMAR units for each eye. Higher logMAR values indicate lower visual acuity. In the case of per patient VA, the value recorded was that of the best seeing eye (best VA) or worst seeing eye (worst eye). VA was classified into 3 categories of blindness:

- Off-chart: when considered “by eyes”, the corresponding eye is not able to identify characters on the ETDRS chart at a 1-metre distance; when considered “per patient” neither eye is able to identify characters on the ETDRS chart at a 1-metre distance.
- Legally blind: patient/eye is on-chart but VA is logMAR 1.0 or higher (between values of 1.0 logMAR and 1.68 logMAR)
- Non-legally blind: patient/eye logMAR < 1.0

Analysis of VA was performed as VA blindness category changes and VA logMAR value changes.

Efficacy measures. The therapeutic response has been evaluated by established outcome measures for LHON, the **Clinically Relevant Benefit (CRB)** either as

- A recovery component; Clinically Relevant Recovery (CRR), defined as
  - Improvement from off-chart VA to at least 1.6 logMAR value, or
  - Improvement of at least 0.2 logMAR value within “on-chart” VA.
  - A patient had a CRR if at least 1 eye had CRR.

or

- A prevention of deterioration component: Clinically Relevant Stabilisation (CRS), which applies to VA when not yet at the “severe blindness” stage.
  - maintenance of VA <1.0 logMAR at Baseline.
  - A patient had a CRS if at least 1 eye had CRS.

Statistical methodology. VA outcomes were compared to a matching external untreated Natural History control group with cases obtained independently from LEROS from multinational centres. The same variables collected over a similar duration of observation were selected to achieve a consistent, random, sample group of sufficient size. A defined matching procedure produced comparable samples with respect to time since disease onset. **Eyes from the Natural History group were selected as comparators if they were close to the average time since onset of the LEROS eyes.** The resulting groups (LEROS and Natural History comparator patients) possessed similar demographic characteristics.

The primary endpoint was analysed using a logistic regression model. The binary response was used as the dependent variable. Independent variables included treatment group (Raxone®-treated patients versus untreated control group) and mutation (G11778A, G3460A, T14484C). **Continuous data** were summarised using the number of observations (N), mean, standard deviation (SD), standard error of the mean (SEM), median, 1st and 3rd quartiles, minimum and maximum. **Categorical data** were presented in contingency tables with frequencies and percentages. P- values < 0.05 were considered statistically significant. Unless otherwise stated, all tests were performed as 2-sided tests, and 2-sided 95% confidence intervals (CI) were produced for the treatment differences. There were no deviations from the planned statistical analyses. All patients who had at least 1 post-Baseline assessment at 12 ± 3 months after Baseline were included in the primary analysis. A sensitivity analysis assessing the impact of incomplete data was performed with a generalised linear mixed model. VA outcomes for patients treated with Raxone® >1 year after onset of symptoms in the last eye were compared to the natural history outcomes from untreated external control patients and to the VA outcomes for patients treated with Raxone® ≤1 year after onset of symptoms. Safety data were analysed using descriptive statistics.

Results of the analysis of efficacy

Primary endpoint

Proportion of eyes that achieved CRB at Month 12 in those patients that started treatment with Raxone® ≤1 year after the onset of symptoms, *compared to eyes in the matching external NH control group*:

CRB was obtained by 60/142 (42.3%) of eyes from LEROS patients compared to 40/193 (20.7%) of eyes from natural history (NH) patients corresponding to a 104% relative improvement compared to spontaneous CRB observed in the control NH eyes. The estimated difference between treatment was statistically significant in favour of Raxone®, presenting an Odds Ratio (OR) of 2.286 [95% confidence limits 1.352, 3.884], OR p-value 0.0020).

The result was corroborated by **sensitivity analysis,** with imputation of missing data, inverse probability of treatment, and an extension of the observation window to 12 ± 3.5 months and 12 ± 4 months. The estimated difference between treatment was maintained with a p-value between <0.0001 and 0.0062 in favour of Raxone®, presenting with OR values between 2.028 and 2.2980.

Secondary endpoints
Proportion of eyes with CRR of VA from Baseline at Month 12 compared to matching external NH control group (component of the primary endpoint).
CRR was observed in 33.1% of eyes from LEROS patients and 18.1% of eyes from NH patients. The estimated difference between treatment resulted in an OR [95% CI] of 1.646 [0.929, 2.918] and a p-value of **0.0873** in favour of Raxone®.

Proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at Month 12 (CRS) compared to matching external NH control group (component of the primary endpoint).
CRS was observed in 64.5% of eyes from LEROS patients and 22.5% of eyes from NH patients. The estimated difference between treatment resulted in an OR [95% CI] of 7.323 [2.339, 25.912] and a statistically significant p-value of 0.0005 in favour of Raxone®.

*Proportion of eyes with CRB in patients treated with Raxone® **>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 external NH control group.*
CRB was observed in 50.3% eyes of LEROS patients and 38.6% eyes of NH patients. The estimated difference between the 2 groups was statistically significant in favour of Raxone®, presenting a p-value of 0.0087 and OR [95% CI] of 1.925 [1.179, 3.173].

Proportion of eyes in patients treated with Raxone® ≤1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained following 6, 18, and 24 months of treatment with Raxone® compared to matching external NH control group.
The proportion of LEROS eyes with CRR showed a steady increase over time (Month 6 25.9%, Month 18 48.1%, Month 24 52.9%), while NH eyes presented a less consistent behaviour (Month 6 17.0% CRR, Month 18 41.4%, Month 24 36.0%). The comparison between treatments presented a significant p-value of 0.0313 and an OR [95% CI] of 2.082 [1.074, 4.099] in favour of Raxone® at the month 24 assessment. So, only the factor 'mutation' was significant over all time-points while the factor 'treatment' only reached significance for month 24.

Results obtained in the ITT population
Visual acuity by eye
Subacute LEROS patients
- There was worsening of VA during the first 6 months post start of treatment, followed by a recovery over the 24 months' follow-up.
- At the last treatment visit, there were fewer eyes "off-chart" and 'legally blind', while the rate of eyes with VA logMAR < 1.0 increased from 25.7% to 36.4%.
- Regarding the timeline after month 6, the rate of eyes with VA logMAR < 1.0 showed a constant increase up to 24 months, thereby justifying long treatment durations.

Chronic LEROS patients
- Worst VA values were present at Baseline, a subsequent nadir did not crystallise.

- The proportion of eyes not legally blind was comparable to the cohort with a disease duration of < 1 year, while the rate of eyes with VA logMAR 1.0 – 1.68 was lower.
- Within the first 6 months of treatment the rate of eyes with VA logMAR < 1.0 and logMAR 1.0-1.68 starts to increase.
- Over the entire 24 months of treatment, there was a progressive migration of eyes towards improved VA categories. The benefit was documented until the last treatment period of month 18 to 24.

Overall, the rates for all 3 VA categories at the end of month 24 was comparable in both groups.

Evolution of logMAR values. In subacute patients, 50% of the eyes (median) presented 1.37 logMAR at Baseline, at month 6 median VA worsened to 1.49 logMAR, improving to logMAR 1.21 at month 24. At the 24-month visit, there was a wide range of VA (-1.80 logMAR - 1.84 logMAR). In chronic patients, there was a continuous improvement over 24 months without detectable nadir. At the 24-month visit, maximum gain was -1.84 logMAR, and maximum loss 0.60 logMAR.

*Change from baseline in best eye VA by follow-up visit***.** In subacute patients, at 6 months, at least 50% had no VA change (median 0.00). The range indicates that some patients profited as early as month 6, while others deteriorated by a maximum VA change of logMAR 1.70. At 24 months, median change from Baseline was -0.14 logMAR) with a maximum improvement of -1.78 logMAR vs. a maximum worsening of 1.84 logMAR). Chronic patients had a median improvement from Baseline of -0.04 logMAR at month 6. At month 24, the median improvement was logMAR -0.08, with a maximum improvement from Baseline of -1.24 logMAR and a maximum decline of 0.12 logMAR. It is to note that the range of change in best eye VA narrowed continuously over 24 months due to a decline in maximum deterioration.

Summary of efficacy

- LEROS met its primary endpoint of CRB (a composite of CRR or CRS) after a treatment of 12 months in a population of LHON patients with a genetically confirmed mtDNA mutation with Raxone® 3x300 mg/day orally started within 12 months after symptom onset (subacute patients).
- The first of secondary endpoints (CRR, a component of the primary endpoint) did not reach the significance level, while the other CRB component CRS (second secondary endpoint) was met.
- The third secondary outcome measure of CRB in chronic patients (disease duration of up to 5 years after onset in the most recent eye) after 12 months of treatment was met.
- The beneficial effect was independent of gender, age, severity of vision loss, and duration of the disease.
- During the second 12 months of treatment, the CRR rate further increased continuously in subacute and chronic patients. In subacute patients, the proportion of LEROS eyes with CRB increased constantly from month 6 to month 24, while the course was less consistent in NH eyes. Factor analysis yielded significant results only for the factor of ‘mutation’ across all time-points, while the influence of the factors ‘treatment’ and ‘gender’ were only significant for month 24.
- In chronic patients, there appears to be a deterioration of VA from month 12 to month 18, followed by an improvement until month 24, which became evident for several outcome measures such as e.g. *VA of eyes (blindness categories)*, *evolution of logMAR values over time*, *change from baseline in VA of eyes at each FU visit,* or *CRR in chronic eyes/patients with off-chart VA at baseline*.
- It is to note that the NH control cohort also experienced some spontaneous benefit. Nevertheless, CRR rate was significantly higher at 24 months in subacute LEROS patients vs. NH controls.
- The applicant states that the results obtained for eyes ≤ 1 year since onset and eyes > 1 year since onset of symptoms support the importance of starting treatment as soon as LHON is diagnosed, irrespective of whether the eye(s) is(are) in the acute or chronic stage.
- LEROS does not answer the question about maintained treatment beyond 24 months of continued therapy, or treatment in patients after 5 years since onset of symptoms.

6.3.2 Key supportive studies

6.3.2.1 RHODOS observational follow-up study (SNT-II-003-OFU)

RHODOS-OFU was a single-visit, observational follow-up study of patients who participated in RHODOS, designed to provide additional data on disease progression following discontinuation of study treatment, and to allow an assessment of the persistence of any benefit in VA obtained from Raxone® treatment during RHODOS.

- Of the 85 RHODOS participants, 60 were enrolled (41 Raxone® and 19 placebo-treated patients). 58/60 provided valid VA data (Raxone®: 39; placebo: 19) and were included in the Efficacy Population. Five patients reported the use of idebenone as prior and concomitant medication between the end of RHODOS and RHODOS-OFU.
- Time since end of RHODOS (Week 24) and enrolment into RHODOS-OFU (OFU) was 30.7±4.9 months (range: 20.9-42.5 months).

Results. Both RHODOS treatment groups showed almost identical (i.e. parallel) improvements in the RHODOS-OFU Study primary endpoint of ‘change in best VA between Week 24 and OFU’ reflecting a parallel change during the off-medication period with maintenance of the therapeutic benefit in the verum arm from Week 24 to open follow-up (OFU).

6.3.2.2 Expanded Access Program (EAP)

LHON patients who reported onset of vision loss within 1 year prior to enrolment were eligible to participate in the EAP performed in Europe, Australia, New Zealand, and the US. Raxone® dosing was at the discretion of the treating physician, but was generally 900 mg/day (300 mg t.i.d, as used in RHODOS). **Outcome measures** were defined as VA data prior to Raxone® initiation (Baseline Visit) and at 3-monthly intervals thereafter. According to updated EAP Results as of October 2021, 87 patients with 173 affected eyes were included. CRR from VA nadir during treatment follow-up was achieved at 6 months in 15.6%, at 12 months in 24.9% of eyes, at 24 months in 35.3%, at 36 months in 38.7%, and at the last visit, in 38.7% of eyes. Regarding the magnitude of recovery in 67 eyes with CRR from VA nadir at time of CRR and at the last observation, the median gain in letters at CRR was 17 (min-max: 10-81), and the median gain in letters at last visit was 32 (min-max: 10-90).

6.3.3 Other relevant efficacy data

6.3.3.1 Case Record Survey (CRS) for Natural History of LHON

The CRS, initiated in May 2013 and performed at 11 study sites in the EU and the US, focused on the

- clinical course of vision loss and
- extent and time course of spontaneous VA recovery

in untreated patients with a genetically confirmed diagnosis of LHON in order to establish an external control group for comparison with RHODOS and EAP data.

Study data. CRS data included year of birth, gender, LHON genotype, onset of first symptoms (for both sides), and previous use of idebenone, including start and stop dates.

Study population. 383 LHON patients with 3128 visual acuity (VA) assessments.

Final Natural History Population. This CRS subgroup included VA data (890 VA assessments) from 106 patients not previously included in RHODOS or the EAP who carried 1 of the main 3 genotypes and who had a first VA (Presentation) assessment conducted within 2 years after LHON onset.

These data were used to establish the natural course of change in VA over time in untreated LHON patients.

Natural History Outcomes Population. The proportion of patients with spontaneous clinically relevant recovery (sCRR) or stabilisation (no post-presentation worsening) of VA was derived from VA data from 74 patients (774 VA assessments) who provided at least 1 further VA assessment conducted within ≥3-24 months of presentation. sCRR or stabilisation were defined in analogy to the terms 'CRR' and 'no-worsening' in RHODOS and in the EAP.

Statistical analysis. To allow a comparison with similar EAP outcome measures, endpoints were analysed at Presentation, at VA nadir, and at the last observation (outcome) for the proportion of subjects in the VA categories of logMAR <1.0 (not legally blind, up to moderate VA loss), logMAR 1.0-1.68 (severe to profound VA loss), and off-chart VA.

Outcome measures. CRS **primary endpoint** was defined as the **VA change with time since onset of symptoms.** The main **secondary endpoint** referred to the **proportion of patients with spontaneous clinically relevant recovery (sCRR) from VA nadir** analysed by disease history and mutation status.

Study population and demographics. VA data from 890 assessments made within 2 years after LHON onset were obtained in 106 patients. Patient demographics of the Natural History Population analysed for this endpoint were representative of the disease with respect to mean age at onset (32.1 years), gender bias (80.2% male), and genotype distribution (G11778A: 73.6%, G3460A: 16.0%, T14484C: 10.4%).

Results

Development of symptoms over time. There was evidence for a rapid and profound vision loss early in the course of the disease:

- **55% of eyes were reported to have deteriorated to logMAR ≥1.0 (the threshold for legal blindness) within 1 week of onset, increasing to 73% within 3 months. After 1 year, more than 80% of eyes were legally blind**.

Prognosis. VA loss was not commonly recovered. Of the 142 observations available in the interval 12 to 24 months after onset, 78% of eyes were legally blind.

Extent of visual loss. The mean nadir was found to be logMAR 1.3 (Snellen 20/400) reached about 6 months after LHON onset.

Spontaneous clinically relevant recovery (sCRR) of VA from nadir in the Natural History Outcomes Population. Applying the same criteria of CRR as used previously, the rates of spontaneous CRR (sCRR) were assessed.

- **sCRR of VA from nadir was observed in 31.1% patients and in 24.3% of eyes.**
- **sCRR rates differed between genotypes**.
- The mean time from Onset to sCRR was 9.9 months (median 7.0), with the shortest mean time observed for the T14484C genotype.

6.4 Safety

6.4.1 Overall safety database

As the current application relies on the MA provided by EMA in the EU, safety data already assessed by EMA are briefly presented at the end of this chapter. As LEROS has not been part of the original proposal or the annual update reports to EMA (report dates 10/2021) and includes long-term safety data up to 24 months of treatment in a larger LHON patient cohort, LEROS safety data have been discussed in detail.

6.4.1.1 LEROS

Safety population

198 patients treated with Raxone® were further subdivided according to treatment duration with all of them receiving treatment on Day 1. The mean duration of exposure was 589.17 days (SD 246.578, SE 17.524, median: 721.9, Q1: 543.00, Q3: 730.00, range: 1-806 days). 170 (85.9%) received treatment for > 6 months, 154 (77.8%) for > 12 months, 149 (75.3%) for > 18 months, and 106 (53.5%) for > 24 months.

Adverse events (AEs)

154/198 (77.8%) of patients reported 891 TEAEs, with 11.3% of these events being considered as product-related (reported in 24.7% of all patients). AEs were mostly of mild or moderate severity. 25/891 events were severe (6.6% of all patients), and 44/891 events were serious not leading to death (reported in 13.6% of all patients). 5.1% of patients discontinued permanently from the study due to TEAEs, and 10.6% interrupted the treatment temporarily. A TEAE leading to death was reported in a single subject.

Analysis of adverse events

AEs were reported by ≥4 (2%) patients in the LEROS Safety Population. The most commonly reported AEs were headache (37 (18.7%) patients), nasopharyngitis (33 [16.7%] patients), and diarrhoea (19 [9.6%] patients).

Severity of TEAEs. 89.1% of AEs were mild, 8.1% moderate, and 2.8% severe.

PTs considered of severe intensity. Cardiac arrest, visual impairment, multiple organ dysfunction syndrome, hepatic failure, hypogammaglobulinaemia, appendicitis, hepatitis C, thermal burn, urine urobilinogen increased, ketoacidosis, metabolic acidosis, delirium, suicidal ideation, acute kidney injury, miscarriage of partner (1 [0.1%] event in each case), ALT increased (0.3% of AEs), AST increased (0.2% of AEs), gGT increased (2 [0.2%] events, suicide attempt (3 [0.3%] events).

System Organ Classes (SOCs) of AEs considered related to Raxone® treatment (N=101). Gastrointestinal disorders (3.1% of AEs), Investigations (4.0%), Nervous system disorders (1.0%), General disorders and administration site conditions (0.7%), Renal and urinary disorders (0.7%), Psychiatric disorders (0.4%).

Deaths. One patient experienced a fatal hepatic failure (Death due to alcoholic liver failure) that was considered to be unrelated to Raxone®.

Table 1: Treatment-emergent adverse events by Preferred Term reported by ≥4 (2%) patients (Safety Population) (CSR LEROS, page 102f)

Preferred Term	Events F=891 f (%)	Patients N=198 n (%)	Days in treatment*		
			Rate	Mean (SD)	Min, max
Total	891 (100.0%)	154 (77.8%)	0.17	247.0 (234.9)	1.0 – 1027.0
Headache	131 (14.7%)	37 (18.7%)	0.28	259.0 (230.3)	1.0 – 760.0
Nasopharyngitis	51 (5.7%)	33 (16.7%)	0.65	217.2 (213.5)	1.0 – 714.0
Diarrhea	28 (3.1%)	19 (9.6%)	0.68	142.8 (212.0)	1.0 – 705.0
Alanine aminotransferase increased	18 (2.0%)	17 (8.6%)	0.94	276.8 (239.2)	19.0 – 734.0
Blood creatine phosphokinase increased	17 (1.9%)	15 (7.6%)	0.88	219.8 (226.3)	22.0 – 734.0
Nausea	20 (2.2%)	15 (7.6%)	0.75	135.2 (183.3)	1.0 – 714.0
Aspartate aminotransferase increased	14 (1.6%)	14 (7.1%)	1.00	256.7 (241.3)	33.0 – 734.0
Oropharyngeal pain	22 (2.5%)	14 (7.1%)	0.64	258.5 (203.1)	4.0 – 718.0
Abdominal pain upper	14 (1.6%)	13 (6.6%)	0.93	80.4 (126.9)	1.0 – 479.0
Cough	14 (1.6%)	12 (6.1%)	0.86	232.6 (218.6)	4.0 – 698.0
Gamma-glutamyltransferase increased	10 (1.1%)	10 (5.1%)	1.00	246.3 (211.2)	19.0 – 561.0
Back pain	13 (1.5%)	9 (4.5%)	0.69	91.2 (106.6)	9.0 – 363.0
Depression	9 (1.0%)	9 (4.5%)	1.00	330.0 (273.4)	15.0 – 682.0
Abdominal pain	10 (1.1%)	8 (4.0%)	0.80	247.5 (258.7)	1.0 – 727.0
Fatigue	8 (0.9%)	8 (4.0%)	1.00	170.3 (256.0)	4.0 – 748.0
Influenza	9 (1.0%)	8 (4.0%)	0.89	233.4 (172.1)	7.0 – 473.0
Sinusitis	8 (0.9%)	7 (3.5%)	0.88	142.8 (228.8)	1.0 – 695.0
Toothache	14 (1.6%)	7 (3.5%)	0.50	339.4 (163.6)	53.0 – 671.0
Rash	7 (0.8%)	6 (3.0%)	0.86	228.6 (279.8)	7.0 – 739.0
Vomiting	7 (0.8%)	6 (3.0%)	0.86	306.4 (308.5)	3.0 – 707.0
Blood triglycerides increased	6 (0.7%)	5 (2.5%)	0.83	325.7 (268.9)	96.0 – 720.0
Dizziness	6 (0.7%)	5 (2.5%)	0.83	157.7 (126.0)	3.0 – 288.0
Dyspepsia	9 (1.0%)	5 (2.5%)	0.56	283.2 (210.7)	37.0 – 751.0
Eye pain	5 (0.6%)	5 (2.5%)	1.00	75.6 (58.8)	15.0 – 171.0
Malaise	5 (0.6%)	5 (2.5%)	1.00	50.6 (65.9)	1.0 – 154.0
Pyrexia	6 (0.7%)	5 (2.5%)	0.83	190.7 (124.3)	29.0 – 377.0
Upper respiratory tract infection	7 (0.8%)	5 (2.5%)	0.71	440.0 (295.6)	32.0 – 716.0
Urinary tract infection	6 (0.7%)	5 (2.5%)	0.83	373.3 (266.7)	43.0 – 644.0
Visual impairment	5 (0.6%)	5 (2.5%)	1.00	257.8 (290.2)	30.0 – 748.0
Anxiety	4 (0.4%)	4 (2.0%)	1.00	368.5 (329.7)	16.0 – 733.0
Bacterial test positive	4 (0.4%)	4 (2.0%)	1.00	188.3 (129.9)	32.0 – 350.0
Blood cholesterol increased	4 (0.4%)	4 (2.0%)	1.00	241.8 (223.5)	35.0 – 545.0
Bronchitis	6 (0.7%)	4 (2.0%)	0.67	122.8 (64.8)	42.0 – 238.0
Gastroenteritis	5 (0.6%)	4 (2.0%)	0.80	167.2 (161.4)	23.0 – 395.0
Influenza like illness	5 (0.6%)	4 (2.0%)	0.80	221.6 (229.4)	17.0 – 577.0
Insomnia	4 (0.4%)	4 (2.0%)	1.00	113.0 (155.6)	2.0 – 338.0
Nasal congestion	7 (0.8%)	4 (2.0%)	0.57	365.0 (204.9)	157.0 – 594.0
Neutrophil count decreased	4 (0.4%)	4 (2.0%)	1.00	215.8 (251.3)	1.0 – 548.0
Pain	4 (0.4%)	4 (2.0%)	1.00	219.8 (350.5)	21.0 – 743.0
Protein urine present	5 (0.6%)	4 (2.0%)	0.80	275.6 (213.5)	91.0 – 616.0
Somnolence	4 (0.4%)	4 (2.0%)	1.00	53.5 (87.2)	1.0 – 183.0

Serious adverse events (SAEs)

SAEs reported by ≥ 2 patients were within the following SOCs: **Infections and infestations (4.0% of patients), nervous system disorders (2.5%), psychiatric disorders (2.5%), investigations (1.5%), cardiac disorders (1.0%),** general disorders and administration site conditions (1.0%), injury, poisoning and procedural complications (1.0%), metabolism and nutrition disorders (1.0%).

SAEs experienced in > 1 subject. SAE of ALT (listed) increased was reported in 2 (1%) of subjects (mean days of treatment: 97 days SD 110.3, range 19-175 days). Suicide attempt (unlisted) was documented in 3 (1.5%) patients (mean days of treatment: 513 days SD 302.2, range 166-718 days).

Selection of SAEs reported in 1 subject each. AST increased (listed), CPK increased, gGT increased (listed), urobilinogen urine increased, ketoacidosis, metabolic acidosis, epilepsy, syncope, depression, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

Adverse events leading to permanent treatment discontinuation

AEs leading to permanent treatment discontinuation in > 1 subject. AE of ALT increased led to discontinuation in 2 (1.5%) of subjects (mean days of treatment: 73.5 days SD 55.9, range: 34-113 days), AE of AST increased was reported in 2 (1.5%) subjects (mean days of treatment: 73.5 days SD 55.9, range: 34-113 days).

Selection of AEs leading to permanent treatment discontinuation reported in 1 subject each. CPK increased, neutrophil count decreased, WBC count decreased, drug reaction with eosinophilia and systemic symptoms, rash maculo-papular.

Adverse events of special interest (AESI)

Abnormal liver function test or hepatitis and blood count abnormalities were considered as **AESIs** per protocol and important potential risks for Raxone® that were closely monitored during LEROS.

46 AEs related to **abnormal liver function tests or hepatitis** (ALT increased, AST increased, bilirubin increased, gGT increased, liver function tests increased, AP increased, hepatitis) were retrieved: 25/46 considered as related to Raxone® administration by the investigator (2/25 SAEs). 6/46 were considered as SAEs (including 1 fatal event).

29 AEs related to **blood count abnormalities** (WBC count decreased, neutrophil count decreased, lymphocytes decreased, eosinophils decreased, platelets decreased, anaemia related laboratory abnormalities, MCV increased, lymphocytes increased, neutrophils increased, were retrieved): 2/29 considered as related to Raxone® administration. There were no SAEs related to blood count abnormalities.

Narratives of SAEs

Two out of 31 non-fatal SAE cases were considered by the investigator to be related to Raxone® treatment:

- One case of gGT and ALT increased. Narrative is indecisive with respect to causality.
- One case with toxic skin eruption, maculopapular rash, and drug reaction with eosinophilia and systemic symptoms 6 days after Raxone® start in a patient with a history of allergic skin reaction to the nonsteroidal anti-inflammatory drug (NSAID) cream-gel and rheumatoid arthritis. Since histological examination confirmed a toxidermia lesion, early-stage drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome could not be excluded. The AE resolved upon Raxone® withdrawal. An additional review of the Santhera safety database for DRESS, toxidermia, and maculopapular exanthema or similar reactions did not reveal any additional events or concerns.

Other significant adverse events related to study medication

38 cases with non-serious AESIs were retrieved from the Global Safety Database (including 1 serious case reporting both an SAE which was not related, but 2 non-serious AESIs which were considered as related; see below).

15/38 cases with non-serious AESIs were considered as related by the Investigator and/or the Sponsor. 14 AESIs in these 15 cases were related to hepatic disorders (elevated transaminases (12), bilirubin increased (2)), and 1 AESI to haematological abnormalities (WBC count decreased). Additional AEs in these 15 cases with AESIs refer to CPK increased after exercise and 3 episodes of metabolic acidosis that were attributed to the clinical syndrome of LHON. Both AEs were assessed as unrelated to Raxone® treatment.

Analysis and discussion of deaths, other SAEs, and other significant AEs

46 SAEs were reported in a total of 32 valid cases that were cumulatively received by the Sponsor's Drug Safety and Pharmacovigilance department. Six reported SAEs in the safety database were related to abnormal liver function test or hepatitis-related AESIs. There was no suggestion of any previously unknown adverse events related to idebenone.

LEROS safety conclusions. Among 198 patients treated with Raxone®, a total of 46 AEs (6/46 SAEs) were related to "Abnormal liver function test" or "hepatitis", and 29 AEs (0/29 SAEs) were related to "Blood count abnormalities" reported in 36 patients (based on data retrieved from the Safety Database). **From the data provided so far, major new safety concerns have not been identified during LEROS.**

6.4.1.2 Other safety data obtained in LHON patients

CHMP concluded that the safety profile of idebenone can be considered benign (Assessment Report EMA/191284/2013). Safety data obtained in other clinical studies in LHON are briefly summarised below, followed by a short analysis of the safety data received from postmarketing surveillance and the EAP in LHON.

6.4.1.2.1 Safety data obtained in other clinical studies in LHON

RHODOS (SNT-II-003)

Phase 2 study, including 85 LHON subjects, aged 14-66 years (55 subjects in the 900 mg/day Raxone®, 30 subjects in the placebo arm). 7 subjects discontinued from the study (3 on Raxone® (1 due to AE, 2 withdrew consent) and 4 on placebo).

Throughout the 24-week treatment period, subjects completed a Patient Diary. Safety was assessed at every visit by evaluation of TEAEs, physical examination, vital signs, electrocardiogram (ECG), clinical laboratory evaluation of haematological and biochemical parameters (blood and urine samples), and urine pregnancy tests for women of childbearing potential. Concentrations of idebenone and its metabolite QS10 were measured at Baseline (pre-dose), Week 12, and Week 24.

Exposure. Mean exposure was 192.0 days (SD 36.1) in the Raxone®-treated group and 197.4 days (SD 17.6) in the placebo group

AEs. 89.1% of subjects in the Raxone®-treated group and 86.7% of subjects in the placebo group experienced AEs. AEs with a difference in incidence > 1 (1.8%) in idebenone than placebo treated subjects were reported in the SOCs of cardiac disorders (9.1% Raxone® versus 0% placebo; these were mainly due to ECG readings at 1 site), ear and labyrinth (7.3% versus 0%), eye disorders (7.3% versus 3.3% each), and psychiatric disorders (7.3% versus 3.3% each).

AEs related to study treatment. In the Raxone®-treated group, 4 subjects (7.3%) had AEs considered related to treatment by the Investigator. AEs in the Raxone® group were related to abnormal liver function test, mild left ventricular hypertrophy, Wolff-Parkinson-White syndrome, and increased blood triglycerides (1 (1.8%) each).

SAEs. Two subjects experienced SAEs both considered unrelated to treatment.

- One subject in the Raxone® group had infected epidermal cyst requiring hospitalisation
- One subject in the placebo group experienced epistaxis (the subject was treated for hypertension).

Severe AEs. Two severe AEs were reported, both in the Raxone® group:

- headache (not related to treatment)
- abnormal liver function test (possibly treatment-related, led to study discontinuation).

AEs leading to discontinuation. One subject withdrew due to severe abnormal liver function tests (see above) after 35 days of 900 mg/day idebenone treatment.

Investigations. There was no evidence for an effect of Raxone® on any haematological or clinical chemistry parameters. No clinically relevant, treatment-related findings were observed for vital signs or ECGs. Four subjects had AEs of left ventricular hypertrophy (LVH), all reported by the same investigational site on the basis of the ECG readings and where the diagnosis was not supported by clinical or ultrasound evidence. These events were not considered to represent a safety signal.

RHODOS-OFU (SNT-II-003-OFU)

60 LHON subjects who previously participated in RHODOS (41 subjects treated with Raxone®, 19 subjects with placebo) were enrolled in this single visit, observational, follow-up study. Time since end of RHODOS and enrolment into RHODOS-OFU was 30.7 ± 4.9 months (mean ± SD; range: 20.9 - 42.5 months). Five patients reported the use of idebenone as prior and concomitant medication between the end of RHODOS and RHODOS-OFU. Patients' current medical status was assessed and, if any medical condition was detected at the visit, the seriousness and potential causal and temporal relationship with intake of RHODOS study medication were determined. A fundoscopic examination as well as an assessment of vital signs were performed.

SAE. There was 1 SAE of hypertensive emergency reported in RHODOS-OFU not related to Raxone®.

Investigations

- Vital sign mean values (systolic and diastolic blood pressure, heart rate, respiratory rate), body weight, and mean changes from Baseline of RHODOS were generally similar for the Raxone® and the placebo groups, both during RHODOS and RHODOS-OFU.

Conclusion. Overall, there was no evidence for novel safety signals in LHON patients previously enrolled into the Raxone® or placebo groups of RHODOS.

6.4.2 Other relevant safety aspects: Overdose

No case of overdose was reported in any of the clinical studies.

6.5 Final clinical benefit-risk assessment

LHON is an inherited condition leading to severe visual loss, mostly affecting both eyes with a limited chance of spontaneous recovery. The majority of cases is contingent upon 3 distinct mutations of the mitochondrial DNA (mtDNA), leading to oxidative stress and final apoptosis of retinal ganglion cells. A minority of cases is due to other mtDNA mutations or autosomal-recessive mutations of the nuclear DNA.
LHON usually starts in 1 eye with the second eye following within several months, leading to severe bilateral visual loss. The various LHON genotypes are characterised by a variable chance of spontaneous recovery. There is currently no cure for LHON, although specific gene therapies are currently being developed for single genotypes. Raxone® is thought to bypass complex I metabolism of the respiratory chain thereby reducing oxidative stress with no respect to the underlying mutation.
The current MAA pertains to LHON patients > 12 years of age regardless of the underlying genotype. Swissmedic has reviewed the current MAA, taking into account the EMA decision of 25 June 2015 (CHMP Assessment Report EMEA/H/C7003834) for Raxone® for the treatment of LHON. As part of post-authorisation measures (PAMs), the CHMP demanded an Open Label study. This study, named LEROS, was completed in August 2021. Upon request, the final CSR of LEROS was submitted to Swissmedic in January 2022. Swissmedic has reviewed LEROS data in detail.

Efficacy. In RHODOS, 53 patients with a disease duration of ≤ 5 years treated with Raxone® for 24 weeks were compared to 28 patients treated with placebo. For the primary endpoint, *best recovery in VA (*defined as the result from the eye experiencing the most positive improvement in VA using ETDRS charts between Baseline and Week 24 in either the right or left eye), there was a trend, but no significant difference between both arms after 24 weeks. For the main secondary endpoint, *change in best VA* (defined as the difference between best VA in either the left or right eye compared to the VA in the best VA at Baseline), there was a statistically significant difference: while there was a worsening between baseline and Week 24 for patients on placebo, Raxone® treated subjects showed a small improvement in best VA.
LEROS compared the data for subacute (onset ≤ 1 year in the most recent eye) and chronic (onset > 1 year and ≤ 5 years) LHON patients carrying 1 of the 3 main mtDNA mutations aged 14 years or older. LEROS results corroborate the efficacy of Raxone® in the promotion of recovery and prevention of worsening in LHON patients with disease onset < 5 years in the most recent eye. Even in case of secondary worsening after the initiation of treatment, beneficial effects were reliably shown with continuous treatment. The comparison of the benefit with Natural History data obtained during Case Report Surveys by the applicant further suggests a beneficial treatment effect for Raxone® exceeding expected spontaneous clinically relevant recovery by chance only.
Additional post hoc analyses requested by the agency for the primary and secondary endpoints in subacute and chronic eyes showed that the benefit for the overall group was mainly driven by the most frequent genotype G11778A and did not result from skewed distribution of the genotype with the best natural prognosis T14484C. Efficacy results were significant and consistent for G11778A across all time-points. As the numbers for the rarer genotypes G3460A and T14484C were limited, treatment benefits for these mutations cannot be finally assessed. Overall, the data support treatment of subacute (onset ≤ 1 year) and chronic (onset > 1 year) eyes for up to 24 months. Efficacy data for treatment durations of more than 24 months are not available. Similarly, the potential responsiveness of other LHON genotypes to Raxone® treatment remains unclear due to restrictions on the genotypes included in the development programme.

Safety. In the LEROS study, 198 LHON patients treated with 900mg/day Raxone® experienced a total of 46 AEs (6/46 SAEs) related to “abnormal liver function test” or “hepatitis” and 29 AEs (0/29 SAEs) related to “blood count abnormalities” reported in 36 patients (based on data retrieved from the Safety Database). There were no cases fulfilling Drug Induced Liver Injury (DILI) criteria. In the RHODOS study, 1 LHON subject withdrew due to severe abnormal liver function tests after 35 days of 900 mg/day idebenone treatment. Four AEs of suicidal attempts and suicidal ideation were reported in 3 individuals during the LEROS study.

Overall, LEROS results confirm the overall benign safety profile for Raxone®. There was no evidence for new, hitherto unknown, safety issues. Established hepatic risks of Raxone® are appropriately addressed in the information for healthcare professionals.
Limitations. Renal or hepatic dysfunction as well as pregnancy/lactation were excluded from study participation in the LHON study programme. Moreover, overlap syndromes of LHON mutation carriers with other mitochondrial disorders have been reported. The latter may develop life-threating liver problems with exposure to certain hepatotoxic drugs. Regarding the limited number of LHON patients treated with Raxone® to date, additional precautions such as testing of liver parameters have been included in the information for healthcare professionals.

Paediatric population. Regarding the paediatric population, RHODOS included subjects from the age of 14 years and a body weight of 45 kg. The open label LEROS study included 13 patients ≤ 1 year after the onset of symptoms and 13 patients > 1 year after the onset of symptoms. There is actually no reason to assume less efficacy for paediatric LHON as compared to adult patients. Therefore, the extrapolated benefit-risk profile for patients > 12 and < 18 years is positive.

Overall conclusion. The final benefit-risk balance of Raxone® for the applied indication (treatment for LHON in patients > 12 years of age with a disease duration of < 5 years in the most recent eye for a maximum of 24 months) is positive.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Raxone was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Raxone 150 mg, film-coated tablets

Composition

Active substances

Idebenone.

Excipients

Core tablet: Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K25, magnesium stearate, colloidal silica. Sodium content: 2.49 mg.
Coating: macrogol 3350, poly(vinyl alcohol), talc, titanium dioxide, sunset yellow FCF (E110) (1.275 mg).

Pharmaceutical form and active substance quantity per unit

Each film-coated tablet contains 150 mg idebenone.

Indications/Uses

Raxone is indicated for the treatment of visual impairment in adolescent patients from 12 years of age and adult patients with Leber’s Hereditary Optic Neuropathy (LHON) (see section “Properties/Effects”).

Dosage/Administration

Treatment should be initiated and supervised by a physician with experience in LHON. The effect of the drug should be regularly monitored by the treating physician.

Usual dosage

The recommended dose is 900 mg/day idebenone (300 mg, 3 times a day). Data regarding continuous treatment with idebenone for up to 24 months are available as part of a Natural History controlled open label clinical trial.

Special populations

Elderly patients

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

Patients with hepatic disorders

Patients with transaminase (aspartate aminotransferase (AST), or alanine aminotransferase (ALT)) elevations greater than three times the upper normal limit were excluded from the post-approval open-label study LEROS, while a very limited number of patients with hepatic disorders was carried out in a non-interventional post-authorisation safety study PAROS. However, no specific posology recommendations can be made. Caution is advised in treatment of patients with hepatic disorders, since adverse events have resulted in temporary interruption or discontinuation of treatment. Patients with transaminase elevations greater than three times the upper normal limit should not receive treatment since use in these patients has not been studied (see section “Warnings and Precautions”).

Patients with renal disorders

Patients with creatinine elevations greater than three times the upper normal limit were excluded from open-label post-approval study LEROS, while a very limited number of patients with renal disorders was investigated in the non-interventional post-authorisation safety study PAROS. However, no specific posology recommendations can be made. Caution is recommended when treating patients with renal impairment, since adverse events have resulted in temporary interruption or discontinuation of treatment. Patients with creatinine elevations greater than three times the upper normal limit should not receive treatment since use in these patients has not been studied (see section “Warnings and Precautions”).

Children and adolescents

The safety and efficacy of Raxone in LHON patients under 12 years of age have not been established. Currently available data are described in sections “Properties/Effects” and “Pharmacokinetics”, but no recommendation on posology can be made.

Mode of administration

Raxone film-coated tablets should be swallowed whole with water. The tablets should not be broken or chewed. Raxone should be administered with food because food increases the bioavailability of idebenone.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

Monitoring

It is recommended that patients are regularly monitored for visual acuity and response to therapy; (e.g., every 3-6 months for the first year and every 6-12 months from then on). Monitoring laboratory evaluations of hepatic function in patients with hepatic impairment (see section “Patients with hepatic disorders”) and laboratory evaluations of renal function, in patients with renal impairment (see section “Patients with renal disorders”) is recommended.

Patients with hepatic disorders

Data from interventional studies with idebenone in patients with hepatic impairment are limited. In the open-label post-approval study LEROS, patients with elevations of more than three times the upper limit of normal transaminases were excluded. Idebenone is completely metabolised prior to excretion and therefore hepatic impairment can have an effect of the plasma levels of idebenone and its metabolites. Caution should be exercised when patients with hepatic impairment are treated with idebenone. A specific dose recommendation cannot be given. For this reason, it is recommended that transaminase (ALT and AST) values are assessed before starting treatment with Raxone (see section “Monitoring”). Patients with transaminase elevations greater than three times the upper normal limit should not receive treatment since use in these patients has not been studied.

Patients with renal disorders

Data from interventional studies with idebenone in patients with renal impairment are limited. In open-label post-approval study LEROS, patients with elevations of more than three times the upper limit of normal creatinine were excluded. Idebenone is not excreted unchanged into urine and therefore renal impairment is not expected to have a major impact on plasma levels of idebenone. However, as metabolite levels may increase, caution should be exercised when idebenone is administered to patients with renal impairment. A specific dose adjustment cannot be recommended. For this reason, it is recommended that creatinine values are assessed before starting treatment with Raxone (see section “Monitoring”). Patients with creatinine elevations greater than three times the upper normal limit should not receive treatment since use in these patients has not been studied.

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.
Sodium
This medication contains less than 1 mmol (23 mg) of sodium per tablet, i.e., it is essentially "sodium-free"

Interactions

The activity of idebenone as a reversible and time dependent inhibitor of cytochrome P450 was investigated in human liver microsomes and idebenone was showed to be a moderately potent reversible inhibitor of all the cytochrome P450 isoforms investigated but there was no evidence of the time dependent inhibition. The order of inhibitory potency from greatest to least was CYP2B6 > CYP1A2 > CYP3A4 (midazolam) > CYP2C19 > CYP3A4 (testosterone) > CYP2C8 > CYP2C9 > CYP2D6 (IC50 values range from 3.06 to 13.5 µM).
Under the current assay conditions with the *in vitro* test systems utilised in this study, idebenone has been determined to be an inhibitor of probe substrate transport mediated via BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2, with a range of IC50 values from 2.36 µM (OCT2) to 27.8 µM (OATP1B3).

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 also weakly inhibit CYP2D6 or CYP2C19 *in vivo*.
In vivo studies confirmed no effect of idebenone on the pharmacokinetics of fluvoxamine, lithium and donepezil.
The strong CYP1A2 inhibitor fluvoxamine did not affect the idebenone metabolic profile. Donepezil caused a small increase in idebenone plasma concentrations, which is not considered clinically relevant.
Small but most probably not relevant changes in the pharmacokinetics of Amitriptylinic caused by the coadministration of idebenone cannot completely be ruled out by the results of a study in healthy volunteers. The high incidence rate of adverse events were mainly caused by reports of tiredness, a symptom most typically observed after treatment with Amitriptyline. Idebenone administered alone was equivalent to idebenone co-administered with donepezil as measured by AUC0-24H and C_{max} for

the major metabolites conjugated idebenone and conjugated QS-10. AUC0-24H and C_{max} for unconjugated idebenone were slightly higher after co-administration. Donepezil administered alone was equivalent to donepezil co-administered with idebenone, as measured by AUC0-24H and C_{max}. Overall, all adverse events and other safety observations demonstrated non-significant rates and trends in keeping with the previous history of the drug in clinical trials and post-marketing experience.

Pregnancy, 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.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of idebenone in the maternal milk. A risk to the breastfed child cannot be excluded. 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.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions to idebenone among patients over 12 years of age were: headaches (12%), rhinopharyngitis (11%), mild to moderate diarrhoea (usually not requiring the discontinuation of the treatment) (8%), increased levels of alanine aminotransferase (7%) and gamma-glutamyltransferase (5%).
The following adverse reactions emerging from clinical trials (RHODOS, LEROS and PAROS) and/or as part of the post-marketing service (PMS) in LHON patients aged 12 and older are tabulated below. A total of 476 subjects had been treated with idebenone for LHON during clinical trials, of which 411 were adult patients and 65 were aged 12 to 18 years old.
Frequency groups are defined according to the following convention:

- Very common (≥1/10);

- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);
- Rare (≥1/10,000 to <1/1,000);
- Very rare (<1/10,000),
- Not known (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders

Common: decreased neutrophil count, increased white blood cell count

Uncommon: anemia, macrocytic anemia, thrombocytopenia, decreased white blood cell count

Cardiac disorders

Uncommon: coronary artery disease

Ear and labyrinth disorders
Common: earache
Uncommon: vertigo

Infections and infestations
Very common: nasopharyngitis
Common: bronchitis, gastroenteritis, sinusitis, upper respiratory tract infections, urinary tract *infections,* influenza
Uncommon: ear infection

Eye disorders

Common: visual impairment, eye pain

Uncommon: photopsia, photophobia, ocular hyperaemia, conjunctival hyperaemia, glaucoma, cataract, dry eyes, conjunctivitis.

Vascular disorders

Common: hypertension

Uncommon: hot flushes

Metabolism and nutrition disorders
Common: folate deficiencies, vitamin B12 deficiencies, vitamin D deficiencies, blood cholesterol increased, blood triglycerides increased

Uncommon: blood uric acid increased

Nervous system disorders
Very common: headache
Common: dizziness
Uncommon: epilepsy

Respiratory, thoracic and mediastinal disorders
Common: cough, nasal congestion, oropharyngeal pain
Uncommon: epistaxis

Gastrointestinal disorders
Common: diarrhoea, abdominal pain, superior abdominal pain, constipation, dyspepsia, vomiting, nausea, toothache
Uncommon: gastritis

Hepatobiliary disorders
Common: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased,
Uncommon: biliary lithiasis, hepatocellular insufficiency, hepatic steatosis, increase in alkaline phosphatase, increase in blood bilirubin
Unknown frequency: hepatic cytolysis*.

Investigations
Unknown frequency: increase in lactate dehydrogenase*.

Skin and subcutaneous tissue disorders
Common: rash
Uncommon: hypersensitivity, drug hypersensitivity syndrome or DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)

Musculoskeletal and connective tissue disorders
Common: back pain, arthralgia, syndrome Gougerot-Sjögren, blood creatine phosphokinase increased
Uncommon: myalgia

Renal and urinary disorders

Common: chromaturia, blood creatinine increased

General disorders and administration site conditions
Common: malaise, fatigue, influenza like illness, pyrexia
Uncommon: shivering, pain

Psychiatric disorders
Common: adjustment disorder with depressed mood, depression, anxiety, insomnia
Uncommon: suicidal tentative, panic attack, hallucination
Not known: suicide *

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Uncommon: anogenital warts, chronic myeloid leukaemia, leukaemic retinopathy, prostate cancer stage IV, skin papilloma, tonsil cancer
Not known: adenoid cystic carcinoma*, malignant neoplasm of unknown primary site*, metastases to lung*

**These adverse effects have been exclusively reported as part of post-marketing service (PMS). Their frequency is unknown*

Collectively, the safety profile of Raxone in patients with LHON when used under conditions of routine clinical care observed in the long-term study PAROS was similar to the precedent open-label study (LEROS) and no new safety concerns were identified.

Friedreich's ataxia (FA)
Raxone has also been evaluated in three pivotal randomized, double blind, placebo controlled studies (IONIA, MICONOS, NICOSIA) conducted in patients with Friedreich's ataxia (FA) which is an indication not authorized in Switzerland. However, adverse events reported in patient support programs are reported.
In the IONIA study a total of 70 subjects ≥8 and <18 years of age at baseline were enrolled and randomized in a 1:1:1 ratio, with 22 subjects receiving 450/900 mg/day idebenone, 24 subjects receiving 1350/2250 mg idebenone and 24 subjects receiving placebo. The mean exposure was similar in all three groups ranging from 168.8 days to 169.9 days. The most frequently treatment-related AEs were abdominal pain upper (six subjects; 13%), nausea, fatigue and headache (five subjects each; 10.8%), diarrhea (four subjects; 8.7%), chromaturia (three subjects; 6.5%), and abdominal pain, dizziness and pollakiuria (two subjects each; 4.34%). Overall, treatment-related AEs were more frequently reported with 1350/2250 mg/day idebenone (58.3% of subjects) than with

450/900 mg/day idebenone (27.3%) or with placebo (45.8%), thus showing no direct relationship to the dose administered.
In the NICOSIA study a total of 48 subjects ≥9 and <18 years of age at baseline were enrolled and randomized 1:1:1:1 in 1 of the 4 treatment arms: low dose idebenone (60 mg ×1 TID), 12 subjects; mid dose idebenone (150 mg × 1 TID), 13 subjects; high dose idebenone (150 mg × 3 TID), 12 subjects; and placebo, 11 subjects. The range of duration of dosing was 171 to 192 days for the combined idebenone group. The most common treatment related AE in the combined idebenone-treated group was headache, experienced by a total of 10 subjects (27%). Other most commonly observed treatment related AEs in the combined idebenone-treated group were diarrhea, nausea (6 subjects each, 16.2%), and dyspepsia (4 subjects each, 10.8%).
In the Miconos study a total of 232 subjects 8 years of age or older were randomized in a 1:1:1:1 ratio, with 57 subjects randomized to 180/360 mg/day idebenone (low dose), 57 randomized to 450/900 mg/day idebenone (mid dose), 59 subjects randomized to 1350/2250 mg idebenone (high dose) and 59 subjects randomized to placebo. The overall mean (SD) exposure for all subjects was 354.7 (54.9) days. The most frequently reported treatment-related AEs were (in order of decreasing frequency in the idebenone treatment groups as a whole) headache (25 subjects, 14.5%), diarrhea (22 subjects, 12.7%), nausea (19 subjects, 11.0%), vomiting (11 subjects, 6.4%), nasopharyngitis (9 subjects, 5.2%), and abdominal pain upper, back pain and cough (eight subjects each, 4.6%).
Cumulatively a total of 256 patients 8 years of age or older and with confirmed diagnosis of FA were exposed to doses of idebenone up to 2250 mg/day divided in 3 oral doses.

The safety profile observed in these patients was consistent with that observed in the LHON population.

Haematological and lymphatic system disorders
Common: anaemia, microcytic anaemia, lymphadenopathy, decreased blood haemoglobin, decreased white blood cell count

Cardiac disorders

Common: angina pectoris, arrhythmia

Infections and Infestations

Very common: lower respiratory tract infection, flu

Common: pharyngitis, tonsillitis, upper respiratory tract infections, pneumonia, viral infection, viral gastroenteritis

Metabolism and nutrition disorders

Common: decreased appetite, muscle cramp

Immune system disorders

Common: hypersensitivity

Reproductive system and breast disorders

Common: dysmenorrhea

Respiratory, thoracic and mediastinal disorders

Very common: cough

Common: dyspnoea, epistaxis, pharyngolaryngeal pain

Gastrointestinal disorders

Very common: diarrhoea, nausea, vomiting, upper abdominal pain

Common: gastritis, oesophagitis, flatulence

*Hepatobiliary disorders**

Common: increased blood bilirubin

Unkown: fulminant hepatitis*, hepatic cytolysis*, jaundice (ocular)*, cholestasis*

Skin and subcutaneous tissue disorders

Common: maculopapular rash, pruritus, allergic dermatitis

Uncommon: angioedema

Musculoskeletal and connective tissue disorders

Very common: back pain, pain in extremities

Common: musculoskeletal chest pain, musculoskeletal pain, myalgia

General disorders and administration site conditions

Very common: fatigue

Common: chest pain, asthenia, pain, oedema

Nervous system disorders

Common: dizziness, migraine, syncope

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon: fibroadenoma of breast, thyroid cancer, thyroid neoplasm, uterine leiomyoma

** These adverse events were reported as part of various "patient support programs".*

Paediatric Population

The tolerability of Raxone at a dose of 900 mg/day divided in 3 oral doses was studied in three clinical studies (Rhodos, Leros and Paros) on 65 paediatric LHON patients aged 12 and above or reported exclusively in post-marketing experience (PMS). The following adverse effects were reported more frequently in these studies than in the general LHON population treated with Raxone.

Haematological and lymphatic system disorders
Common: macrocytosis, leukopenia, neutropenia, increased neutrophil count, increased eosinophil count

Cardiac disorders
Common: left ventricular hypertrophy

Ear and labyrinth disorders
Common: inner ear disorders, vertigo

Eye disorders
Common: stye, ocular hyperemia

Gastro-intestinal disorders
Common: viral gastro-enteritis, abdominal migraine, misaligned teeth
Not known: endobrachyoesophagus (Barrett's esophagus)*, eosinophilic esophagitis*

Hepatobiliary disorders
Common: increased blood bilirubin, increased alkaline phosphatase

General disorders and administration site conditions
Common: chest pain

Immune system disorders
Common: anaphylactic shock, drug hypersensitivity, hypogammaglobulinemia, seasonal allergy

Infections and infestations
Common: streptococcal pharyngitis, vulvovaginitis, viral infection

Investigations
Common: decreased appetite

Musculoskeletal and connective tissue disorders
Common: musculoskeletal chest pain, neck pain, pain in the extremities, myalgia

Nervous system disorders
Common: migraine, convulsions, drowsiness, syncope, tremor

Psychiatric disorders
Common: suicide attempts, suicidal ideation, irritability

Reproductive organs and breast disorders
Common: dysmenorrhea

Renal and urinary disorders
Common: proteinuria

Respiratory, thoracic and mediastinal disorders
Common: pulmonary congestion, superior airways congestion, allergic bronchitis, dyspnea, wheezing

* These adverse effects have been exclusively reported as part of post-marketing (PMS). Their frequency is unknown.

The safety and efficacy of Raxone in patients with LHON of less than 12 years old have not been yet established. Due to the rarity of the disease, it was not possible to obtain sufficient data from controlled clinical studies with idebenone in paediatric LHON patients of less than 12 ans.

Raxone has also been evaluated in clinical studies conducted in pediatric patients with FA (indication not authorized in Switzerland) at doses up to 2250 mg/day divided in 3 oral doses on 293 paediatric patients from 12 years of age and 38 patients under 12 years of age with Friedreich's Ataxia (FA). The safety profile of Raxone in the paediatric population is comparable to that in the general population of patients with FA with the exception of the following adverse events:

Patients 12 years of age and older:
Very common: pyrexia, myalgia and vertigo.

Patients under 12 years of age:
Very common: gastroenteritis, dyspepsia, gastroesophageal reflux, abdominal pain, pyrexia, pain, ear infection, arthralgia, muscle cramp, vertigo, chromaturia, pharyngolaryngeal pain, and rash.

Common: enteritis, streptococcal pharyngitis.

Pharmacokinetic studies in patients aged 8 years and older with Friedreich's ataxia did not reveal significant differences in the pharmacokinetics of idebenone in the paediatric population.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No report of overdose has been received from the RHODOS and the PAROS studies.
Overall three cases occurred during the post-marketing experience for LHON treatment, with maximum overdose ranged between 1050mg/day to 1500mg/day taken erroneously for up to several weeks. All events were non-serious and were not associated with clinical symptoms.
There is no specific antidote for idebenone. When needed, supportive symptomatic treatment should be given.

Properties/Effects

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.

Pharmacodynamics

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

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).

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 or placebo for a period of 24 weeks (6 months). Raxone was given as 3 daily doses of 300 mg 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 (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	

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 may be maintained.

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 for a period of 24 months. Raxone was given as 3 doses of 300 mg daily, each with meals. ·An external, natural history (NH) control cohort was created using retrospective data from two LHON case record surveys. The LEROS ITT population was used to evaluate efficacy endpoints for which no comparisons were made to the NH cohort. When direct comparisons were made, the modified ITT (mITT; n=181) population was used, which only included patients who carried one of the three ‘common’ pathogenic mitochondrial DNA (mtDNA) mutations. Applying the mITT inclusion/exclusion criteria to the NH cohort, 372 patients were eligible for matching. A matching algorithm, approved by the European Medicines Agency (EMA), guaranteed

that the time from onset of symptoms to the baseline assessment was comparable between the final NH control dataset and that of the mITT at each analysis timepoint
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 ≤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. The estimated difference between treatment and control was statistically significant (p-value 0.0020) in favour of Raxone 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 >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 favour of Raxone presenting a p-value of 0.0087 and OR [95% CI] of 1.925 [1.179, 3.173].

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 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.

Paediatric population

In RHODOS and the EAP (expanded access program) 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, nine patients under 14 years of age were included and received Raxone at 900 mg/day.
Due to the rarity of the disease, it has not been possible to obtain sufficient data from controlled clinical trials with idebenone in paediatric patients with LHON.

Pharmacokinetics

Absorption

Food increases the bioavailability of idebenone by approximately 5-7-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 as demonstrated in a study to evaluate the metabolism and disposition of idebenone in normal, healthy adult male volunteers

following oral administration of a single dose of the drug. 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. The plasma protein binding is 98.5%.

Metabolism

In a study to evaluate the metabolism and disposition of idebenone in normal, healthy adult male volunteers following oral administration of a single dose of the drug, idebenone underwent extensive first pass metabolism. Major metabolite pathways included oxidative side chain cleavage and conjugation with glucuronic acid and sulfate.
Idebenone's major metabolic pathways are the quinone reduction of idebenone via the cytoplasmatic enzyme NADH-quinone oxidoreductase (NQO) to form the hydroquinone (Ide-HQ) and the oxidation to form QS10, which can either happen through CYP enzymes or via alcohol dehydrogenase (ADH) and subsequent aldehyde dehydrogenase (ALDH). QS10 is converted to an acyl-CoA thioester that undergoes fatty acid β-oxidation to the acyl-CoA thioester of the chain-shorted metabolites QS8, QS6 and QS4. None of these metabolites are active. Ide-HQ, QS10, QS8, QS6 and QS4 are further metabolised via conjugation. The major human metabolites in plasma are Ide-HQ conjugates and in urine QS4-conjugates. The conjugated metabolites show considerably higher plasma concentrations than the parent compound idebenone. They are eliminated more slowly and accumulate moderately upon repeated administration (1.2 to 1.7-fold).

Elimination

Idebenone is completely metabolised prior to excretion into urine (79.8%) and faeces (7.1%). The major metabolites in urine are QS4 conjugates, which accounted for 60% of administered idebenone dose. In a study to evaluate the metabolism and disposition of idebenone in normal, healthy adult male volunteers following oral administration of a single dose of the drug, biliary secretion and enterohepatic circulation may also have been important in the disposition of idebenone.

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.

Kinetic for specific patient groups

Hepatic impairment

The pharmacokinetics of idebenone metabolites were studied in 12 male patients with mild to moderate hepatic impairment (n=5 Child-Pugh Score A, n=7 Child-Pugh Score B) and 31 healthy subjects at comparable age. The study confirmed that patients were able to metabolise idebenone and a moderate increase in idebenone conjugates and a prolongation of its half-life was observed. The plasma levels of QS10 conjugates were clearly increased in patients with hepatic impairment and the half-life of these metabolites prolonged about 3-fold.

Renal impairment

The pharmacokinetics of idebenone metabolites were studied in 12 male patients with impaired renal function (creatinine clearance <40 mL/min/1.73 m2), 2 male patients with renal failure requiring haemodialysis, and 41 healthy subjects at comparable age to the patients. Patients with impaired renal function showed moderately higher levels of idebenone conjugates compared with healthy volunteers and patients on haemodialysis showed very similar plasma concentrations of these metabolites compared with healthy volunteers. The levels of QS conjugate were in general comparable across the study populations with slightly higher AUC values in patients with renal impairment and on haemodialysis compared to healthy subjects.

Children and adolescents

Whilst clinical trials experience in paediatrics with LHON under 12 years old is limited, 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.

Preclinical 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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store at room temperature (15-25°C).
Keep out of the reach of children.

Authorisation number

68063

Packs

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

Marketing authorisation holder

Chiesi SA, Villars-sur-Glâne

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October 2022