

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

Raxone 150 mg film-coated tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 150 mg idebenone.

### Excipients with known effect

Each film-coated tablet contains 46 mg of lactose (as monohydrate) and 0.23 mg of sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Film-coated tablet.

Orange, round, biconvex film-coated tablet of 10 mm diameter, engraved with '150' on one side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

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

### **4.2 Posology and method of administration**

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

#### Posology

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

Data regarding continuous treatment with idebenone for up to 24 months are available as part of a Natural History controlled open label clinical trial (see section 5.1).

#### Special populations

##### *Elderly*

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

##### *Hepatic or renal impairment*

Patients with hepatic or renal impairment have been investigated. However, no specific posology recommendations can be made. Caution is advised in treatment of patients with hepatic or renal impairment, since adverse events have resulted in temporary interruption or discontinuation of treatment (see section 4.4).

In the absence of sufficient clinical data, caution should be exercised in patients with renal impairment.

#### *Paediatric population*

The safety and efficacy of Raxone in LHON patients under 12 years of age have not yet been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on posology can be made.

#### Method of administration

Raxone 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.

### **4.3 Contraindications**

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

### **4.4 Special warnings and precautions for use**

#### Monitoring

Patients should be regularly monitored according to local clinical practice.

#### Hepatic or renal impairment

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

#### Chromaturia

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

#### Lactose

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

#### Sunset yellow

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

### **4.5 Interaction with other medicinal products and other forms of interaction**

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

*In vivo* idebenone is a mild inhibitor of CYP3A4. Data from a drug-drug interaction study in 32 healthy volunteers indicate that on the first day of oral administration of 300 mg idebenone t.i.d., the metabolism of midazolam, a CYP3A4 substrate, was not modified when both medicinal products

were administered together. After repeated administration  $C_{max}$  and AUC of midazolam were increased by 28% and 34%, respectively, when midazolam was administered in combination with 300 mg idebenone t.i.d. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozone, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving idebenone.

Idebenone may inhibit P-glycoprotein (P-gp) with possible exposure increases of, e.g., dabigatran etexilate, digoxin or aliskiren. These medicines should be administered with caution in patients receiving idebenone. Idebenone is not a substrate for P-gp *in vitro*.

#### 4.6 Fertility, pregnancy and lactation

##### Pregnancy

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

##### Breast-feeding

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

##### Fertility

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

#### 4.7 Effects on ability to drive and use machines

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

#### 4.8 Undesirable effects

##### Summary of the safety profile

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

##### Tabulated list of adverse reactions

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

System Organ Class	Preferred Term	Frequency
Infections and Infestations	Nasopharyngitis	Very common
	Bronchitis	Not known
Blood and lymphatic system disorders	Agranulocytosis, anaemia, leukocytopenia, thrombocytopenia, neutropenia	Not known
Metabolism and nutrition disorders	Blood cholesterol increased, blood triglycerides increased	Not known

<b>System Organ Class</b>	<b>Preferred Term</b>	<b>Frequency</b>
Nervous system disorders	Seizure, delirium, hallucinations, agitation, dyskinesia, hyperkinesia, poriomania, dizziness, headache, restlessness, stupor	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Very common
Gastrointestinal disorders	Diarrhoea	Common
	Nausea, vomiting, anorexia, dyspepsia	Not known
Hepatobiliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, blood bilirubin increased, hepatitis	Not known
Skin and subcutaneous tissue disorders	Rash, pruritus	Not known
Musculoskeletal and connective tissue disorders	Back pain	Common
	Pain in extremity	Not known
Renal and urinary disorders	Azotaemia, chromaturia	Not known
General disorders and administration site conditions	Malaise	Not known

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

#### **4.9 Overdose**

No report of overdose has been received from the RHODOS, the LEROS and the PAROS studies. Doses up to 2,250 mg/day have been administered in clinical studies showing a safety profile consistent with that reported in section 4.8.

There is no specific antidote for idebenone. When needed, supportive symptomatic treatment should be given.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Psychoanaleptics, Other psychostimulants and nootropics;  
ATC code: N06BX13

#### Mechanism of action

Idebenone, a short-chain benzoquinone, is an anti-oxidant assumed to be capable of transferring electrons directly to complex III of the mitochondrial electron transport chain, thereby circumventing complex I and restoring cellular energy (ATP) generation under experimental conditions of complex I deficiency. Similarly, in LHON idebenone can transfer electrons directly to complex III of the electron transport chain, thereby bypassing complex I which is affected by all three primary mtDNA mutations causing LHON, and restoring cellular ATP generation.

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

### Clinical efficacy and safety

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

In RHODOS a total of 85 LHON patients, 14-66 years of age, with any of the 3 primary mtDNA mutations (G11778A, G3460A or T14484C) and disease duration of not more than 5 years were enrolled. Patients received either 900 mg/day Raxone or placebo for a period of 24 weeks (6 months). Raxone was given as 3 doses of 300 mg daily, each with meals.

The primary endpoint “best recovery of visual acuity (VA)” was defined as the result from the eye experiencing the most positive improvement in VA from baseline to week 24 using ETDRS charts. The main secondary endpoint “change in best VA” was measured as the difference between best VA in either the left or right eye at 24 weeks compared to baseline (Table 1).

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

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

Analysis according to Mixed Model of Repeated Measures

One patient in the placebo group presented with ongoing spontaneous recovery of vision at baseline. Exclusion of this patient yielded similar results as in the ITT population; as could be expected, the difference between idebenone and placebo arm was slightly larger.

\*logMAR - [Logarithm](#) of the Minimum Angle of Resolution

A pre-specified analysis in RHODOS determined the proportion of patients with an eye with baseline VA of  $\leq 0.5$  logMAR in whom the VA deteriorated to  $\geq 1.0$  logMAR. In this small subgroup of patients (n=8), 0 of 6 patients in the idebenone group deteriorated to  $\geq 1.0$  logMAR whereas 2 of 2 patients in the placebo group showed such a deterioration.

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

A *post-hoc* responder analysis was performed in RHODOS evaluating the proportion of patients who had a clinically relevant recovery of VA from baseline in at least one eye, defined as either: (i) improvement in VA from unable to read a single letter to able to read at least 5 letters on the ETDRS chart; or (ii) improvement in VA by at least 10 letters on the ETDRS chart. Results are shown in Table 2 including supporting data from 62 LHON patients using Raxone in an Expanded Access Programme (EAP) and from 94 untreated patients in a Case Record Survey (CRS).

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

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

In the EAP the number of responders increased with longer treatment duration, from 19 out of 62 patients (30.6%) at 6 months to 17 out of 47 patients (36.2%) at 12 months.

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

The primary endpoint in LEROS was the proportion of eyes that achieved a Clinically Relevant Benefit (CRB) (that is, in which there was either a Clinically Relevant Recovery [CRR] of VA from Baseline or a Clinically Relevant Stabilization [CRS]) at Month 12 in those patients that started treatment with Raxone  $\leq$ 1 year after the onset of symptoms, compared to eyes of patients from an external Natural History (NH) control group. CRB was observed in 42.3% of eyes from LEROS patients, in contrast to 20.7% eyes from NH patients. Clinically, this represents a relevant 104% relative improvement compared to spontaneous CRB that may occur in the control NH eyes. The estimated difference between treatment and control was statistically significant (p-value 0.0020) in favor of Raxone 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 favor of Raxone presenting a p-value of 0.0087 and OR [95% CI] of 1.925 [1.179, 3.173].

A total of 198 patients received treatment with Raxone and were included in the Safety Population. The mean duration of treatment in the Safety Population was 589.17 days (range: 1 – 806 days), which was equivalent to a total exposure of 319.39 person-years. A total of 154 (77.8%) of the patients undertook treatment for  $>$ 12 months. A total of 149 (75.3%) patients underwent treatment at the  $>$ 18-month timeframe; at the  $>$ 24-month timeframe, this was 106 (53.5%). A total of 154 (77.8%) patients reported Treatment Emergent Adverse Events. The Adverse Events (AE) reported were mainly of mild or moderate severity; 13 (6.6%) patients who received Raxone treatment reported severe AEs. Forty-nine (24.7%) patients reported AEs that were considered by the Investigator to be treatment-related. Twenty-seven (13.6%) patients experienced Serious Adverse Events and ten (5.1%) had AEs that led to permanent discontinuation of study treatment. No new safety concerns have emerged in patients with LHON enrolled in the LEROS study.

PAROS was a post-authorization non-interventional safety study designed to collect longitudinal safety and effectiveness data in routine clinical settings in patients prescribed with Raxone for the treatment of LHON. This study was conducted at 26 centres in 6 European countries (Austria, France, Germany, Greece, Italy and The Netherlands).

In the long-term safety study PAROS, a total of 224 LHON patients with a median age of 32.2 years at baseline received treatments with Raxone and were included in the Safety population. Over half of the patients (52.2%) had the G11778A mutation; 17.9% had the T14484C mutation, 14.3% had the

G3460A mutation, and 12.1% had other mutations. Time in treatment of these patients is displayed in the table 3 below.

**Table 3: Time in treatment (Safety Population)**

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

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

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

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

There was one death in the study, in an 81-year-old male patient who died of terminal prostate carcinoma, which was assessed by the Investigator as unrelated to Raxone.

No new safety concerns have been identified with long-term treatment with Raxone in patients with LHON when used under conditions of routine clinical care in the PAROS study. The safety profile of Raxone observed in PAROS was similar to that from a previous open-label study (the LEROS study).

#### Paediatric population

In clinical trials in Friedreich's Ataxia, 32 patients between the ages of 8 and 11 years and 91 patients between the ages of 12 and 17 years received idebenone at ≥ 900 mg/day for up to 42 months. In RHODOS and the EAP in LHON, a total of 3 patients between the ages of 9 and 11 years and 27 patients between the ages of 12 and 17 years received idebenone at 900 mg/day for up to 33 months. In PAROS, only nine patients under 14 years of age were included and received Raxone at 900 mg/day.

This medicinal product has been authorised under 'exceptional circumstances'.

This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

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

## **5.2 Pharmacokinetic properties**

### 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. On repeat dosing, maximum plasma concentrations of idebenone are reached on average within 1 hour (median 0.67 h range: 0.33-2.00 h).

### Distribution

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

### Biotransformation

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

### Elimination

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

### Linearity/non-linearity

In phase I pharmacokinetic studies, proportional increases in plasma concentrations of idebenone were observed for doses from 150 mg to 1050 mg. Neither idebenone nor its metabolites showed time-dependent pharmacokinetics.

### Hepatic or renal impairment

No data are available in these populations.

### Paediatric population

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

## **5.3 Preclinical safety data**

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Lactose monohydrate  
Cellulose, microcrystalline  
Croscarmellose sodium  
Povidone (K25)  
Magnesium stearate  
Silica, colloidal anhydrous

#### Film-coating

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

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

5 years.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

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

### **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

Chiesi Farmaceutici S.p.A.  
Via Palermo 26/A  
43122 Parma  
Italy

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1020/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 8 September 2015

Date of latest renewal: 25 June 2025

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Excella GmbH & Co. KG  
Nürnberger Strasse 12  
90537 Feucht  
Germany

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### **• Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## **E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

This being a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<b>Description</b>	<b>Due date</b>
The MAH shall provide yearly updates on any new information concerning efficacy and safety in patients with Leber Hereditary Optic Neuropathy (LHON).	Yearly, simultaneously with submission of Periodic Safety Update Report (when applicable).

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTONS/ HDPE BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

Raxone 150 mg film-coated tablets  
idebenone

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 150 mg of idebenone.

**3. LIST OF EXCIPIENTS**

Contains lactose and sunset yellow FCF (E110). See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

180 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

For oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Chiesi Farmaceutici S.p.A.  
Via Palermo 26/A  
43122 Parma  
Italy

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1020/001

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Raxone 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

<2D barcode carrying the unique identifier included on the Outer Packaging.>

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

<PC {number}  
SN {number}  
NN {number} if applicable nationally >

<Not applicable for the immediate packaging.>

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### Raxone 150 mg film-coated tablets idebenone

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Raxone is and what it is used for
2. What you need to know before you take Raxone
3. How to take Raxone
4. Possible side effects
5. How to store Raxone
6. Contents of the pack and other information

#### **1. What Raxone is and what it is used for**

Raxone contains a substance called idebenone.

Idebenone is used to treat vision impairment in adults and adolescents with an eye disease called Leber's Hereditary Optic Neuropathy (LHON).

- This eye problem is inherited – this means it runs in families.
- It is caused by a problem with your genes (called a “genetic mutation”) that affects the ability of cells in the eye to produce the energy they need to work normally, so they become inactive.
- LHON can lead to loss of eyesight due to the inactivity of cells responsible for vision.

Treatment with Raxone can restore the ability of cells to produce energy and so allow inactive eye cells to work again. This can lead to some improvement in lost eyesight.

#### **2. What you need to know before you take Raxone**

##### **Do not take Raxone**

- if you are allergic to idebenone or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Raxone if:

- you have any blood, liver or kidney problems.

### Change in urine colour

Raxone may make your urine become reddish brown. This change in colour is harmless – it does not mean your treatment needs to change. However, the change in colour could mean that you have problems with your kidneys or bladder.

- Tell your doctor if your urine changes colour.
- He or she may do a urine check to make sure the change in colour is not hiding other problems.

### **Tests**

Your doctor will check your eye-sight before you start taking this medicine and then at regular visits while you are taking it.

### **Children and adolescents**

This medicine should not be used in children This is because it is not known if Raxone is safe or works in patients under 12 years of age.

### **Other medicines and Raxone**

Some medicines may interact with Raxone. Tell your doctor if you are taking, have recently taken or might take any other medicines, especially any of the following:

- antihistamines to treat allergies (astemizole, terfenadine)
- to treat heartburn (cisapride)
- to treat muscle and speech tics associated with Tourette syndrome (pimozide)
- to treat hearth rhythm disorders (quinidine)
- to treat migraine (dihydroergotamine, ergotamine)
- to put you to sleep called “anaesthetics” (alfentanil)
- to treat inflammation in rheumatoid arthritis and psoriasis (cyclosporine)
- to prevent the rejection of an organ transplant (sirolimus, tacrolimus)
- to treat strong pain called “opioids” (fentanyl)

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

- Your doctor will prescribe Raxone to you only if the benefits of the treatment are greater than the risks to the unborn child.
- Raxone may pass into the mother’s milk. If you are breast-feeding your doctor will discuss with you whether to stop breast-feeding or to stop taking the medicine. This will take into account the benefit of breast-feeding to the child and the benefit of the medicine for you.

### **Driving and using machines**

Raxone is not expected to affect your ability to drive or use machines.

### **Raxone contains lactose and sunset yellow (E110)**

- Raxone contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product..
- Raxone contains a colourant called “sunset yellow” (also called E110). This may cause allergic reactions.

## **3. How to take Raxone**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

### **How much to take**

The recommended dose is 2 tablets three times a day - this is a total of 6 tablets per day.

### **Taking this medicine**

- Take the tablets with food - this helps to get more of the medicine from your stomach into your blood.
- Swallow the tablets whole with a glass of liquid.
- Do not crush or chew the tablets.
- Take the tablets at the same time of day each day. For example in the morning at breakfast, with lunch at mid-day and with dinner in the evening.

### **If you take more Raxone than you should**

If you take more Raxone than you should, talk to your doctor straight away.

### **If you forget to take Raxone**

If you forget a dose, skip the missed dose. Take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

### **If you stop taking Raxone**

Talk to your doctor before you stop taking this medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effect may happen with this medicine:

**Very common** (may affect more than 1 in 10 people):

- nasopharyngitis (cold)
- cough

**Common** (may affect up to 1 in 10 people):

- diarrhoea (mild to moderate that usually does not require discontinuation of treatment)
- back pain

**Unknown frequency** (frequency cannot be estimated from the available data):

- bronchitis
- changes in blood test results: low level of white blood cells, or low level of red blood cells, or low level of platelets
- increased cholesterol or fat in the blood –shown in tests
- fits, feeling confused, seeing or hearing things that are not real (hallucinations), feeling excited, movements that you cannot control, a tendency to wonder away, feeling dizzy, headache, feeling restless, dazed and unable to act or think normally
- nausea, vomiting, loss of appetite, indigestion
- high levels of some liver enzymes in the body which mean you have liver problems – shown in tests, high levels of “bilirubin” – this can make your skin and the whites of your eyes look yellow, hepatitis
- rash, itching
- pain in extremity
- high levels of nitrogen in the blood - shown in tests change in urine colour
- generally feeling unwell

### **Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Raxone

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after 'EXP'. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Raxone contains

- The active substance is idebenone. Each film-coated tablet contains 150 mg of idebenone.
- The other ingredients are:  
Tablet core: lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, povidone K25, magnesium stearate and silica colloidal anhydrous.  
Tablet film-coating: macrogol, poly(vinyl alcohol), talc, titanium dioxide, sunset yellow (E110).

### What Raxone looks like and contents of the pack

- Raxone film-coated tablets are orange, round tablets of 10 mm diameter, engraved with '150' on one side.
- Raxone is supplied in white plastic bottles. Each bottle contains 180 tablets.

### Marketing Authorisation Holder

Chiesi Farmaceutici S.p.A.  
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### Manufacturer

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**This leaflet was last revised in**

This medicinal product has been authorised under ‘exceptional circumstances’.

This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

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

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.