EMA/467186/2015

Summary of the risk management plan (RMP) for Raxone (idebenone)

This is a summary of the risk management plan (RMP) for Raxone, which details the measures to be taken in order to ensure that Raxone is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Raxone, which can be found on Raxone's EPAR page.

Overview of disease epidemiology

Raxone is a medicine used to treat Leber's hereditary optic neuropathy (LHON), a rare hereditary disease that can lead to blindness. In Europe it is estimated that not more than 2 people in every 100,000 suffer from this condition. LHON is much more likely to affect males, with almost three-quarters of all patients being male. Although the disorder can develop at any time between childhood and old age, LHON is most likely to occur in young men in their 20s and 30s.

Summary of treatment benefits

Raxone is available as tablets containing the active ingredient idebenone.

Raxone has been investigated in one main study involving 85 patients with LHON, in which it was compared with placebo (a dummy treatment) over 24 weeks. The main measure of effectiveness was improvement in vision, mostly based on the numbers of letters patients were able to read on a standard eye test chart. By the end of the study, patients treated with Raxone were able to read on average 3 to 6 letters more compared with patients receiving placebo. Furthermore, some patients who were classified as 'off chart' (unable to read any letters on the chart) at the beginning of the study were able to read at least one line during the eye test after treatment, and this was also considered clinically important. Additionally, 30% of patients treated with Raxone (16 out of 53) had a clinically relevant recovery of vision in at least one eye, compared with 10% of patients (3 out of 29) in the placebo group.

Additional supportive data on the benefits of Raxone came from an expanded access program which supplied Raxone to individual patients not participating in a clinical study. Supportive data also came from a case record survey which included data from patients without treatment. The analysis of these data showed that generally a larger proportion of patients treated with Raxone had vision improvement compared with untreated or placebo-treated patients.

Unknowns relating to treatment benefits

The safety and effectiveness of Raxone in children under the age of 12 years of age has not been established. Raxone has not been studied in elderly patients, patients who are pregnant or breastfeeding and those with reduced kidney or liver function. In addition, there is limited information on the long-term benefit on eyesight after Raxone has been stopped.

Summary of safety concerns

Important identified risks

There are no important identified risks for Raxone.

Important potential risks

Risk	What is known
Abnormal liver function test and hepatitis (liver disease)	A few reports of changes in liver function tests and hepatitis in people treated with Raxone have been received. Hence this is considered to be a potential risk with Raxone.
Blood count abnormalities	A few reports of abnormalities of blood counts in people treated with Raxone have been received. Hence this is considered to be a potential risk with Raxone.

Missing information

Risk	What is known
Use during pregnancy and breastfeeding	In experimental studies, Raxone has not shown any evidence of harm to unborn animals. However, Raxone has not been tested in pregnant women. Doctors should only prescribe Raxone to women who are pregnant, or who may become pregnant, if the benefits of the treatment to the mother outweigh any risks to the unborn child. Animal studies have shown that Raxone is present in the mother's milk. Raxone may be present in human milk. The doctor and the breastfeeding mother should decide whether to use Raxone while breastfeeding or to stop breastfeeding whilst taking Raxone.
Use in older patients	In clinical studies, Raxone has not been studied in older patients. This is because LHON generally begins at a younger age.
Use in children under 14 years of age	There is limited data for the use of Raxone in LHON in children under 14 years of age. There is therefore limited information on how well it works or what the side effects would be in children under 14 years of age with LHON. However, Raxone has been studied in a different disease (Friedreich's ataxia, an inherited disease of the nervous system and muscles) in younger children and has not shown any major safety concerns
Use in patients with liver impairment	Raxone has not been studied in patients with liver impairment and therefore there is no information as to how well it works in LHON in these patients or what the side effects would be.
Use in patients with kidney impairment	Raxone has not been studied in patients with kidney impairment and therefore there is no information on how well it works in LHON in these patients or what the side effects would be.
Safety of long-term	In the clinical studies patients with LHON were treated for 24 weeks.

Risk	What is known
use in patients with LHON	Therefore there is limited information on the safety of long-term use of Raxone. However, clinical data were collected from an expanded access programme from patients with LHON treated with Raxone for up to 18 months.
Interaction with medicines known as CYP3A4 substrates	Raxone may interact with certain medicines which are altered in the body in a certain way, and thus may increase their toxicity. Doctors should be cautious in using Raxone with products known as 'CYP3A4 substrates'.
Interaction with medicines known as P-gp substrates	Raxone may interact with certain medicines which are broken down in the body in a certain way, and thus may increase their toxicity. Doctors should be cautious in using Raxone with products known as 'P-gp substrates'.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides doctors, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising the risks. Information for patients is available in plain language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Raxone can be found on Raxone's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
A non-interventional study of clinical experience in patients prescribed Raxone for the treatment of LHON (PASS registry SNT-IV-003)	Primary: - To further evaluate the long-term safety profile of Raxone in the treatment of LHON when used in routine clinical practice. Secondary: - To further evaluate the long-term effectiveness of Raxone in the treatment of LHON when used in routine clinical	Long-term safety, use in populations not studied in clinical trials: pregnancy and breastfeeding, elderly, children under 12 years of age, liver impairment, kidney impairment.	Planned	Planned: Interim reports and final study report: To be submitted with annual re-assessments

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	practice. - To quantify discontinuation of treatment due to adverse events or due to lack of therapeutic response or loss of response. - To further learn about the risk of abnormal liver function tests and hepatitis			
Phase I open label study of the potential pharmacokinetic interaction of idebenone (150 mg film-coated tablet) with midazolam in healthy male volunteers.	<u>Primary</u> - To evaluate the pharmacokinetics of midazolam in the presence of idebenone after repeated administration of idebenone as a film-coated tablet. <u>Secondary</u> - To obtain further safety and pharmacokinetic information after repeated administration of idebenone.	Potential for Raxone to block the enzyme CYP3A4	Planned	Final study report: 31 January 2017
External natural history controlled, open-label intervention study to assess the efficacy and safety of long-term treatment with Raxone in LHON (SNT-IV-005)	<u>Primary:</u> - To assess the effectiveness of Raxone, compared with no treatment, in improving vision or in preventing its worsening in patients treated with Raxone less than 1 year after the symptoms appear. <u>Secondary:</u> - To assess the effectiveness of Raxone,	Long term safety and efficacy	Planned	Interim reports: To be provided in annual re-assessments Final study report: 31 August 2020 (to be submitted with the annual re-assessment)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	compared with no treatment, in improving vision or in preventing its worsening in patients treated with Raxone more than 1 year after the symptoms appear. - To compare the effectiveness of Raxone in improving vision or in preventing its worsening in patients treated with Raxone less than1 year and more than 1 year after the symptoms appear. - To assess the influence of mutation on improving vision or preventing its worsening in LHON patients treated with Raxone. - To assess if the effectiveness of Raxone changes depending on the duration between appearance of symptoms and start of Raxone treatment. - To assess the influence of duration of treatment with Raxone on changes in visual acuity in LHON patients. - To assess safety of long-term treatment of LHON patients with Raxone.			
Historical case record survey (CRS) of visual acuity data from	- To establish the clinical course (natural history) and visual acuity outcomes in patients	To provide control group to the open label study	Planned	Interim reports: To be provided in annual re-assessments

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
patients with LHON (SNT-CRS-002)	with a genetically confirmed diagnosis of LHON. - To combine data from this CRS with CRS data collected previously (as reported in SNT-IR-006, NCT01892943) to be used to generate the comparator group for the open-label study SNT-IV-005.			Final study report: 31 August 2020 (to be submitted with the annual re-assessment)
Follow up of patients in the existing expanded access programme (SNT-EAP-001)	To collect further long-term real-world efficacy and safety data.	Long-term safety and efficacy	Ongoing	Interim reports: To be provided in annual re-assessments Final study report: 31 August 2019 (to be submitted with the annual re-assessment)

Studies which are a condition of the marketing authorisation

The following studies are conditions of the marketing authorisation:

- A non-interventional study of clinical experience in patients prescribed Raxone for the treatment of LHON (PASS registry SNT-IV-003);
- External natural history controlled, open-label intervention study to assess the efficacy and safety of long-term treatment with Raxone in LHON (SNT-IV-005);
- Historical case record survey of visual acuity data from patients with LHON (SNT-CRS-002);
- Follow up of patients in the existing expanded access programme (SNT-EAP-001).

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 08-2015.