BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**RAXONE** (idebenone), ophthalmic medicinal product

Insufficient clinical benefit in Leber's hereditary optic neuropathy because of the lack of methodologically acceptable clinical data demonstrating the efficacy of the drug, despite a significant therapeutic need

Main points

- ▶ RAXONE has marketing authorisation in the treatment of visual impairment in adolescent and adult patients with Leber's hereditary optic neuropathy (LHON).
- ▶ There is no demonstration of sufficient methodological quality of the efficacy of idebenone on visual acuity.
- ▶ The tendency to spontaneous improvement of visual acuity is observed in the placebo group in the RHODOS study.
- ▶ The data that suggest efficacy of idebenone in the treatment of patients with LHON are the results of certain post-hoc analyses of efficacy data from the RHODOS study as well as data from the provision of the product.
- ▶ In the absence of demonstration of its efficacy, this medicinal product has no role in the therapeutic strategy.

Therapeutic use

- Currently there is no recommended treatment for managing patients with LHON with visual impairment. Patient management is based on:
- checking for cardiac abnormalities, especially Wolff-Parkinson-White syndrome;
- the implementation of preventive measures including quitting tobacco and alcohol in order to best protect the mitochondrial function of ganglion cells of the retina and optic nerve;
- the use of medicinal products that have not demonstrated efficacy but whose mechanism of action (antioxidant medicines) suggests benefit, such as glutathione, vitamin E or coenzyme Q10;
- the implementation of various useful aids to improve peripheral vision such as magnifying glasses and lenses. Increased lighting is also essential.
- Follow-up by an optometrist or a rehabilitation centre allows faster mobilisation of the vision retained by the patient.
- **Role of the medicinal product in the therapeutic strategy**

In the absence of demonstrated efficacy of RAXONE in the treatment of adult and adolescent patients with LHON, this medicine has no role in the therapeutic strategy.

Clinical data

- The efficacy data for RAXONE rely on the randomised, double-blind, placebo-controlled study RHODOS, which included 85 patients with LHON for less than 5 years. Patients received either oral idebenone 900 mg/day or a placebo for a period of 24 weeks (6 months). The patients included were 14 to 66 years old with a median age of 30, 85.9% (n=73) were male. At baseline, visual acuity for both eyes was particularly poor in both groups: 1.75 logMar in the idebenone group and 1.68 in the placebo group. A total of 46.7% (n=38) were unable to read at least one letter with both eyes. The majority (67.1%, n=57) of patients had a G11778A mutation and 20% (n=17) of patients had a T14484C mutation which can be accompanied by partial spontaneous recovery of visual acuity.

- With regard to the best recovery of visual acuity in one of the two eyes (primary endpoint), the difference between the groups after 24 weeks of treatment compared to baseline, was -0.064 logMar (95% CI [-0.184; 0.055]), equivalent to +3 letters. This difference is neither statistically significant nor clinically relevant.
- With regard to change in best visual acuity regardless of the eye (the main secondary endpoint), there was no statistically significant difference between the groups after 24 weeks of treatment and compared to the initial value: 0.120 logMar (95% CI [-0.25, 0.013]; not significant), equivalent to +6 letters.
- This study was extended by an observational follow-up study that consisted of a single check-up visit and showed that the change in best visual acuity between baseline in RHODOS and the follow-up visit (or 2.5 years of follow-up) was not statistically significant between the idebenone group and placebo.
- The data that suggest efficacy of idebenone in the treatment of patients with LHON are the results of certain post-hoc analyses of efficacy data from the RHODOS study as well as data from the provision of the product. Their level of evidence is therefore very low.

Benefit of the medicinal product

- Despite a significant therapeutic need but given the lack of methodologically acceptable clinical data demonstrating the efficacy of idebenone in the treatment of adolescent and adult patients with LHON, the actual benefit of RAXONE is insufficient for reimbursement by National Health Insurance, awaiting efficacy data from the open-label interventional study to evaluate the efficacy and safety of RAXONE.
- Does not recommend inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".