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NEUROLOGY
New medicinal product
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TRANSPARENCY COMMITTEE OPINION SUMMARY

OCREVUS (ocrelizumab), immunosuppressant

Moderate clinical benefit in early-stage primary progressive multiple sclerosis (PP-MS) in terms of disease duration and degree of disability, associated with imaging data characteristic of inflammatory activity, but no demonstrated clinical advantage in the therapeutic strategy

Main points

- OCREVUS has been granted marketing authorisation for the treatment of early-stage PP-MS in terms of duration of disease and degree of disability, associated with imaging data characteristic of inflammatory activity.
- A single study, conducted on a stringently selected population (age <55 years), detected a modest gain *versus* placebo, whose clinical relevance was not guaranteed: after 120 weeks of treatment, the proportion of patients with disability progression confirmed at least 12 weeks later was 34.0% in the placebo group and 30.2% in the ocrelizumab group, i.e. an absolute difference of less than 4%.
- OCREVUS failed to improve the quality of life of the patients in the study.
- A number of major uncertainties remain concerning the long-term safety of OCREVUS-induced lymphodepletion in this disease that progresses over numerous years.

Pre-existing indication*

OCREVUS has also been granted marketing authorisation for the treatment of adults suffering from active forms of recurrent multiple sclerosis (R-MS) defined by clinical parameters or imaging

Therapeutic strategy

Patient management is based mainly on supportive care (re-education, mechanical assistance, treatment of spasticity, supportive care, etc.). Several off-label medicinal products are also used, in particular rituximab, an anti-CD20 like ocrelizumab.

Role of the medicinal product in the therapeutic strategy

OCREVUS is a first-line treatment for patients with early-stage PP-MS in terms of duration of disease and degree of disability, associated with imaging data characteristic of inflammatory activity. Its efficacy and safety in the most severe forms of PP-MS have not been established; its use should not be considered in patients with advanced disabilities.
Failing any comparative data, the role of ocrelizumab relative to rituximab, another anti-CD20 used in MS-PP, is unknown. A comparative study *versus* rituximab could clarify the role of ocrelizumab in the therapeutic strategy.

Clinical data

* This summary does not cover this indication.

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- The evaluation of ocrelizumab in PP-MS is based on a single phase III, randomised, double-blind study *versus* placebo performed on 732 patients with an early form of the disease. Some patients included in the study did not have imaging data characteristic of inflammatory activity, contrary to that stipulated in the OCREVUS MA.
- After at least 120 weeks of treatment, a higher number of patients from the placebo group than from the ocrelizumab group displayed confirmed progression of disability at 12 weeks (primary endpoint): HR=0.76, CI95% = [0.59; 0.98], p=0.0321. The absolute difference between the two groups, however, was small: after 120 weeks of treatment, the fraction of patients with confirmed progression of disability at 12 weeks was estimated at 34.0% in the placebo group *versus* 30.2% in the ocrelizumab group. No differences were detected in the physical aspect of the SF-36 quality of life score (ranked secondary endpoint).
- A higher number of treatment-related adverse events were reported in the ocrelizumab group (61.5%) than in the placebo group (43.5%). The number of patients diagnosed with malignant tumours during the study was higher in the ocrelizumab group (2.3%, n=11/486) than in the placebo group (0.8%, n=2/239). This potential risk of malignant tumour needs to be monitored in the long-term.
- Phase III clinical development of OCREVUS in MS-PP is also based on the data from a phase II/III study that evaluated rituximab in a less stringently selected population. The primary endpoint for this study was not met and the *post-hoc* analyses suggest a possible effect of rituximab in a population similar to that defined by the MA for OCREVUS. These *post-hoc* analyses, derived from a negative study, were considered as supplementary data for granting the MA for OCREVUS in PP-MS.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for neurology specialists
- Considering the precise indication of the MA, the decision to start or discontinue OCREVUS treatment should be made after consultation of a multiple sclerosis resource and expertise centre accredited in the context of the neurodegenerative diseases plan

Benefit of the medicinal product

- The actual clinical benefit* of OCREVUS is moderate
- OCREVUS does not provide any clinical added value** (CAV V) in the therapeutic strategy for the management of early-stage PP-MS in terms of duration of disease and degree of disability, associated with imaging data characteristic of inflammatory activity
- Approved for hospital treatment

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This document was drafted on the basis of the Transparency Committee opinion dated 11 July 2018 (CT-16833) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) is its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"

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