HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
27 MAY 2020

cladribine
MAVENCLAD 10 mg tablets

reassessment

Key points

Favourable opinion for reimbursement in the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging (MRI) features.

Clinical benefit now low (previously it was insufficient) in this indication.

What therapeutic improvement?

No clinical added value in the management of highly active R-MS.

Role in the care pathway?

As soon as the RR-MS diagnosis has been established, rapid initiation of long-term treatment is recommended to reduce relapse frequency and the progression of the disability in the short term. Several treatment options can be offered as first-line treatment: beta interferons (AVONEX, REBIF, BETAFERON, EXTAVIA, PLEGRIDY), glatiramer acetate (COPAXONE), teriflunomide (AUBAGIO), dimethylfumarate (TECFIDERA) or ocrelizumab (OCREVUS) in case of active R-MS. The choice of treatment should be made based on the safety profile of the medicinal products, the method of administration and patients' preferences.

When the inflammatory activity of the disease, assessed clinically (number and severity of relapses) and by MRI criteria (T1 Gd+ lesions, T2 lesion load, etc.), becomes or remains high, despite first-line long-term treatment, the initiation of a more active treatment is recommended. The following medicinal products may be used as second and later-line treatment, according to the conditions defined by their MA and following consultation of a resource and expertise center:

- Fingolimod (GILENYA) and natalizumab (TYSABRI) have an MA restricted to highly active forms of RR-MS; these are the reference treatments at this stage of the disease,
- Alemtuzumab (LEMTRADA) has been restricted by the Committee to highly active forms of RR-MS despite first or second-line treatment,
- Ocrelizumab (OCREVUS) may also be used in highly active R-MS, if it has not been used as first-line therapy. However, no robust data have assessed its efficacy and safety as an alternative to second-line treatments or in case of failure of these products,
- Finally, mitoxantrone (ELSEP – NOVANTRONE and generics) is a rescue therapy that has an MA in highly active forms of R-MS associated with rapidly progressing disability where no therapeutic alternatives exist.

In rare cases, where RR-MS is severe at the outset and rapidly progressing, treatment with natalizumab or fingolimod may be recommended as first-line therapy in accordance with the MA of these medicinal products.

Role of the medicinal product in the care pathway:

MAVENCLAD (cladribine) is a therapeutic option in patients with highly active R-MS. Its efficacy has only been established versus placebo, in patients with predominantly not very active RR-MS, in terms of annualised relapse rate and imaging criteria. The data in highly active RR-MS are based on post-hoc analyses and no data in highly active forms of SP-MS, included in the MA, are available.

In the absence of comparative data with current treatments for highly active R-MS (natalizumab, fingolimod, alemtuzumab and ocrelizumab) and due to still limited knowledge related to its safety of use, the Committee recommends reserving the use of MAVENCLAD (cladribine) for patients failing to respond to or ineligible for these therapeutic alternatives.

01 COMMITTEE'S CONCLUSIONS

01.1 Clinical benefit

◗ Multiple sclerosis (MS) is a serious, disabling and progressive, chronic neurological disease. It is characterised by inflammation and selective, chronic demyelination of the central nervous system. Its symptoms are multiple: motor and sensory disorders, sensory, bladder, sphincter and sexual deficits, cognitive function and mood disorders. They can considerably reduce patients' autonomy and affect their quality of life. The severity of the disease is very variable, ranging from forms causing little incapacity to forms leading to significant disabilities within a few years.
◗ MAVENCLAD (cladribine) is a medicinal product designed to prevent relapses and the progression of disability.
◗ In highly active forms of R-MS, the efficacy/adverse events ratio of MAVENCLAD (cladribine) is poorly established in view of the clinical data available and, in particular, due to the methodological weaknesses of efficacy and safety data in the population retained by the MA.
◗ There are therapeutic alternatives.
◗ MAVENCLAD (cladribine) is a therapeutic option in patients with highly active R-MS. In the absence of comparative data with current treatments for highly active R-MS (natalizumab, fingolimod, alemtuzumab and ocrelizumab) and due to still limited knowledge related to its safety of use, the Committee recommends reserving the use of MAVENCLAD for patients failing to respond to or ineligible for these therapeutic alternatives.

Public health impact

Considering:
- the severity of highly active forms of R-MS,
- the size of the target population, estimated to be 4,670 patients in France,
- the partially met medical need,
- the lack of evidence to support an improvement in the care and/or life pathway,
- the lack of any demonstrated impact on the organisation of care,
- the lack of response to the identified need (lack of impact on morbidity and mortality and on quality of life),

MAVENCLAD is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of MAVENCLAD is low in the MA indication.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication(s) and dosages.

01.2 Clinical Added Value

Considering:
- **the demonstration of the superiority of MAVENCLAD solely versus placebo in terms of annualised relapse rates and imaging criteria, whereas a comparison versus an active treatment could have been conducted, in a phase III study (CLARITY study),**
- **the comparison conducted mainly in a population of patients with mostly not very active RR-MS (off-label), and the non-robust nature of the available data in highly active RR-MS (post-hoc analysis on 30% of patients in the CLARITY study) who were predominantly (60%) treatment-naïve;**
- **new data submitted based mainly on an observational study, which do not enable to assess the contribution of cladribine insofar as the results come from patients mostly treated off-label;**

- **and the lack of data in patients with highly active SP-MS, nonetheless included in the MA,**

the Transparency Committee considers that MAVENCLAD provides no clinical added value (CAV V) in the management strategy for highly active R-MS.