HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
22 JULY 2020

The legally binding text is the original French opinion version

siponimod
MAYZENT 0.25 mg and 2 mg film-coated tablets

First assessment

Key points

Unfavourable opinion for reimbursement in the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

Role in the care pathway?

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating disease of the central nervous system. Several forms of the disease can be defined, depending on the level of inflammatory activity and the progression of functional disability:

- **relapsing-remitting MS (RRMS)**, characterised by significant inflammatory activity, defined by the occurrence of demyelinating episodes (relapses) localised in the white matter of the CNS, alternating with periods of remission. This is the most common form of MS (80 to 85% of cases).
- **secondary progressive multiple sclerosis (SPMS)**, which is a progressive form of RRMS developing within a median period of 15 to 20 years after the first neurological event and in approximately 50 to 60% of patients with RRMS. These forms are characterised by continuous neurological degeneration, leading to a progression towards irreversible disability, with or without the persistence of inflammatory activity (active and non-active forms).
- and **primary progressive multiple sclerosis (PPMS)**, characterised by continuous and irreversible worsening of disability from the start of the disease, without a remission phase and generally with a lower inflammatory activity.

According to the EMA, the term relapsing MS (RMS) includes patients having presented a single demyelinating event who show dissemination of lesions in time and space on MRI scans, RRMS and SPMS with relapses and excludes PPMS. Among RMS, active forms[1] should be differentiated from highly active forms[2] in accordance with the marketing authorisations of the medicinal products concerned.

The treatment strategy for active SPMS is based on supportive care (rehabilitation therapy, mechanical aids, treatment of spasticity, etc.) to manage the functional disability and on certain medicinal products targeting the residual inflammatory activity of the disease, with no medicinal product having to date demonstrated its efficacy on the medium or long-term progression of disability.

Hence, some β-1b interferons (BETAFERON and EXTAVIA) have an MA for the treatment of active SPMS[3] and other medicinal products are non-specifically indicated in active or highly active RMS (REBIF interferon β-1a, OCREVUS ocrelizumab and MAVENCLAD, cladribine). Medicinal products containing mitoxantrone (ELSEP – NOVANTRONE and generics) also have an MA in the treatment of patients with highly active RMS associated with rapidly evolving disability where no alternative therapeutic options exist.

In addition, other immunomodulatory agents or immunosuppressants are sometimes used off-label for the treatment of active SPMS (rituximab or cyclophosphamide in particular), especially in the first years of the transition to the SP form when the inflammatory activity remains high. Other therapeutic strategies are sometimes developed by the experts. However, there are no robust data confirming the therapeutic benefit of these immunomodulatory agents or immunosuppressants used off-label in these clinical situations.

MAYZENT (siponimod) has no role in the therapeutic strategy for active SPMS in view of the alternatives and available data.

[1] Defined in accordance with the MAs of the medicinal products concerned by relapses or imaging features of inflammatory activity.

[2] Including, according to the MAs of the medicinal products concerned, the following adult patients:

- patients presenting with a highly active form of the disease, despite a complete and well-conducted treatment involving at least one disease-modifying therapy for MS, or
- patients presenting with severe and rapidly progressing RR-MS, defined by two or more incapacitating relapses in one year, combined with 1 or more lesions enhanced after injection of Gadolinium on the brain MRI, or with a significant increase in T2 lesion load compared to a previous recent MRI.

[3] The exact wording of the MAs for BETAFERON and EXTAVIA is: Patients with SPMS with active disease, evidenced by relapses.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Multiple sclerosis (MS) is a serious and disabling, progressive chronic neurological disease. Secondary progressive MS (SPMS), a progressive form of relapsing-remitting MS (RRMS) is characterised by continuous neurological degeneration, leading to a progression towards irreversible disability, with or without the persistence of inflammatory activity (active and non-active forms).
◗ MAYZENT (siponimod) is a medicinal product that aims to prevent the progression of disability related to relapses in active SPMS.
◗ The efficacy/adverse effects ratio has not been adequately established in view of the numerous uncertainties identified (low effect size on worsening of disability evaluated in the short term only (3 months confirmed disability progression) and compared to placebo only, data in the MA indication derived from a subgroup of patients analysed a posteriori, doubt with respect to the internal validity of the study, etc.) (see Summary and Discussion).
◗ There are therapeutic alternatives.
◗ The Committee considers that MAYZENT (siponimod) has no role in the therapeutic strategy for active SPMS in view of the alternatives and available data.

Public health impact:

Considering:
- the seriousness of active SPMS,
- its prevalence estimated to be around 13,500 patients,
- the identified partially met medical need,
- the lack of elements supporting the absence of a deterioration in the care and/or life pathway in the absence of robust quality of life data,
- the absence of any demonstrated impact on the organisation of care,
- the lack of response to the identified need (no expected additional impact of MAYZENT (siponimod) on morbidity and mortality and quality of life),

MAYZENT (siponimod) is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of MAYZENT (siponimod) is insufficient in the MA indication.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.

Clinical Added Value

Not applicable.