HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
2 DECEMBER 2020
The legally binding text is the original French opinion version

ozanimod
ZEPOSIA 0.23 mg + 0.46 mg hard capsules
ZEPOSIA 0.92 mg hard capsules

First assessment

Key points

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

What therapeutic improvement?

No clinical added value in the therapeutic strategy for RRMS on the basis of currently available data.

Role in the care pathway?

Relapsing remitting multiple sclerosis (RRMS) is 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.

As soon as the RRMS 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 first-line therapeutic options may be proposed: beta interferons (AVONEX, REBIF, BETAFERON, EXTAVIA, PLEGRIDY), glatiramer acetate (COPAXONE), teriflunomide (AUBAGIO), dimethylfumarate (TECFIDERA). In the event of active RMS, ocrelizumab (OCREVUS) may be used. The choice of treatment should be made on the basis of the safety profile of the medicinal products, their method of administration and patients' preferences.

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

- Fingolimod (GILENYA) and natalizumab (TYSABRI) have an MA restricted to highly active forms of RRMS,
- Alemtuzumab (LEMTRADA) has been restricted by the Committee to highly active forms of RRMS despite first or second-line treatment,
- Ocrelizumab (OCREVUS) may also be used in highly active RMS (recurrent remittent (RR) or secondary progressive (SP)), if it has not been used as first-line therapy. However, no robust data has assessed its efficacy and safety as an alternative to second-line treatments or in the event of failure of these products,
- Finally, mitoxantrone (ELSEP – NOVANTRONE and generics) is a salvage treatment that has an MA in highly active forms of RMS (RR or SP) associated with rapidly progressing disability where no therapeutic alternatives exist.

It should be noted that ozanimod and fingolimod have not been the subject of a direct comparison, despite having the same pharmacological profile.
In rare cases, where RRMS is severe and rapidly progressing from the outset, treatment with natalizumab or fingolimod may be recommended as first-line therapy in accordance with the MA of these medicinal products. However, the use of alemtuzumab or mitoxantrone should not be considered as first-line therapy in the absence of sufficient data given the frequency of serious adverse events associated with these medicinal products. In addition, the Committee highlights the fact that no robust data is available confirming the therapeutic benefit and safety of use of an induction strategy compared to an escalation strategy.

Stabilisation of the disease under either of these treatments is assessed by the number and severity of residual relapses, as well as the development of new lesions on MRI. There is no robust data assessing the benefit of long-term continuation of these powerful immunosuppressive therapies in stabilised patients. Their safety and efficacy in terms of the prevention of disability in the long term have yet to be established.

Role of the medicinal product in the care pathway

ZEPOSIA (ozanimod) is a first-line treatment option in active forms of recurrent remittent multiple sclerosis.
Its superiority has been demonstrated versus interferon, INF β-1a (AVONEX, 30 µg IM, once weekly) in terms of annualised relapse rate. However, there is no data available demonstrating an effect on the reduction of disability progression.
Its short-term safety profile (median follow-up of 50 months and maximum of 71 months) appears to be acceptable, but there are uncertainties concerning its long-term safety given the known profile of other medicinal products belonging to the S1P receptor modulator family.

There is no comparative data versus the other medicinal products available in the treatment of RRMS, meaning that the drug cannot be positioned compared to these.

Hence, the choice between the various treatments in RRMS should be made on the basis of the safety profile of the medicinal products, their method of administration and patients' preferences. It is also necessary to consider whether patients are planning a pregnancy.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Multiple sclerosis (MS) is a serious and disabling, progressive chronic neurological disease. It corresponds to inflammation and selective, chronic demyelinisation of the central nervous system. The manifestations are multiple: motor and sensory disorders, sensory, bladder-sphincter and sexual disturbances, cognitive function and mood disorders. They can considerably reduce patients' autonomy and impair 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.

◗ ZEPOSIA (ozanimod) is a medicinal product to prevent relapses and progression of disability.

◗ Its efficacy/adverse effects ratio is high.

◗ There are therapeutic alternatives.

◗ It is a first-line treatment in RRMS.

Public health impact

Considering:

- the seriousness of RRMS,
- its prevalence of 143/100,000 in France[1],
- the partially met medical need,
- the partial response to the identified need due to an impact demonstrated solely versus interferon β1-a (30 µg IM, once weekly) on morbidity in terms of reduction in annualised relapse rate, but with no demonstrated impact on slowing down of disability progression, a major objective in the management of this disease,
- the lack of evidence to support an improvement in the care or life pathway,
- the absence of any demonstrated impact on the organisation of care,

ZEPOSIA (ozanimod) is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of ZEPOSIA hard capsules (ozanimod) is substantial 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 and dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **demonstration in two phase 3, randomised, double-blind studies of the superiority of ZEPOSIA (ozanimod) 1 mg compared to interferon, INF β-1a (30 µg IM, once weekly) in terms of reduction in the annualised relapse rate (ARR, primary endpoint), with an absolution reduction of:**
  - **37.7% (CI95% = [23.2-49.4], p < 0.0001) in the RADIANCE B study, with a duration of 24 months, and**
  - **48.3 % (CI95% = [33.7-59.5], p < 0.0001) in the SUNBEAM study, with a duration of 12 months,**

but taking into account the absence of:

- **demonstration of a difference in terms of the disability progression endpoint after 3 months or after 6 months versus interferon (3rd ranked endpoint in the two phase 3 studies), considered to be the most relevant criterion to assess the patient's clinical course,**
- **robust quality of life data, in a disease that causes the progressive disability of patients,**
- **direct comparison with the available alternatives (some of which are more optimal than interferon β-1a (30 µg IM, once per week, study comparator) whereas such a comparison could have been conducted (except in the case of OCREVUS, developed concomitantly) and the results of the indirect comparison meta-analysis, which do not enable an unbiased assessment of the relative positions of the different comparators in the care pathway,**
- **long-term safety data (median follow-up of 50 months and maximum limited to 71 months) leading to uncertainties, particularly given the known profile of other medicinal products belonging to the S1P receptor modulator family,**

the Transparency Committee considers that ZEPOSIA (ozanimod) provides no clinical added value (CAV V) in the care pathway for active forms of RRMS.