HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
2 JUNE 2021

The legally binding text is the original French opinion version

ofatumumab
KESIMPTA 20 mg solution for injection in pre-filled syringe
KESIMPTA 20 mg solution for injection in pre-filled pen

First assessment

Key points

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

What therapeutic improvement?

KESIMPTA (ofatumumab), in the same way as OCREVUS (ocrelizumab), provides:

- A therapeutic improvement compared to teriflunomide (AUBAGIO) in patients with early-stage RRMS in terms of disease duration and inflammatory activity,
- No clinical added value in the management of highly active or severe RMS.

Role in the care pathway?

As soon as the RR (relapsing-remitting) 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 first-line therapeutic options may be proposed: beta interferons (AVONEX, REBIF, BETAFERON, EXTAVIA, PLEGRIDY), glatiramer acetate (COPAXONE), teriflunomide (AUBAGIO), dimethylfumarate (TECFIDERA), ozanimod (ZEPOSIA).

In the event of RMS with active disease, irrespective of the progressive form (RR, SP, PP), ocrelizumab (OCREVUS) may be used as first-line treatment.

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 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, initiation of a more active treatment is recommended. The modified Rio score is validated to assess the response to certain first-line treatments. 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 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 RMS (RR or SP), 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 the event of failure of these products,
- Ozanimod (ZEPOSIA) in the treatment of RR-MS (active, also including the highly active form) in the absence of comparative data versus the other proprietary medicinal products available in the treatment of RR-MS, it is not possible to rank the use of these proprietary medicinal products compared to one another.
- 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.

In rare cases, where RR-MS 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.

<u>Role of KESIMPTA (ofatumumab) in the care pathway</u>:

KESIMPTA (ofatumumab) is a first or second-line treatment in all active forms of recurrent multiple sclerosis (RRMS or SPMS with relapses), in the same way as OCREVUS (ocrelizumab).

Its superiority has been established versus teriflunomide in patients with early-stage RRMS in terms of disease duration and inflammatory activity.

There is no available comparative data versus the other medicinal products available in the first-line treatment of RMS, including anti-CD20 antibodies (rituximab off-label and ocrelizumab), making it impossible to rank it at this stage in the strategy compared to the other products. It should be noted that ocrelizumab could not be used as a comparator in the studies supplied due to its concomitant development with ofatumumab.

A comparative study versus rituximab could clarify the role of ofatumumab in the care pathway.

Hence, the choice between the various treatments in RMS should be made on the basis of the safety profile of the medicinal products, their method of administration and patients' preferences.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Multiple sclerosis (MS) is a progressive and disabling, serious 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.
◗ KESIMPTA (ofatumumab) is a medicinal product to prevent active episodes and progression of disability.
◗ The efficacy/adverse effects ratio is high.
◗ There are medicinal alternatives (see chapter 05. Comparators).
◗ This is a first or second-line treatment in all active forms of recurrent multiple sclerosis (RRMS or SPMS with relapses), in the same way as OCREVUS (ocrelizumab). Its superiority has been established versus teriflunomide in patients with early-stage RRMS in terms of disease duration and inflammatory activity.

Public health impact

Considering:
- the seriousness of RMS,
- the prevalence of MS of 143/100,000 patients in France,
- the partially met medical need,
- the lack of additional response to the identified need due to:
    - no expected additional impact of KESIMPTA (ofatumumab) on morbidity and mortality,
    - no expected impact on quality of life in the absence of robust data,
    - 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 in the absence of data,

KESIMPTA (ofatumumab) is not liable to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of KESIMPTA (ofatumumab) 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 randomised, double-blind phase 3 studies of the superiority of KESIMPTA (ofatumumab) versus teriflunomide, a clinically relevant comparator:
    - in terms of reduction in annualised relapse rate (clinically relevant primary endpoint), with a clinically relevant reduction of 50.5% (CI95% = [0.374; 0.654], p < 0.001) in the ASCLEPIOS I study and 58.5% (CI95% = [0.308; 0.559], p < 0.001) in the ASCLEPIOS II study
    - in terms of reduction of confirmed disability progression at 3 months (HR=0.66, CI95% = [0.50; 0.86], p=0.002) and at 6 months (HR=0.68; CI95% = [0.50; 0.92], p=0.012) (clinically relevant ranked secondary endpoints, subject to a grouped analysis in both studies)
- in a selected population, primarily with early-stage RRMS in terms of disease duration and inflammatory activity,
- the absence of robust comparative data versus the available first-line alternatives, including the other anti-CD20 antibodies, rituximab and ocrelizumab, the latter having been the subject of concomitant development,

and despite:
- the absence of demonstration of a difference in terms of the endpoint of improvement in confirmed disability progression at 6 months versus teriflunomide (third ranked secondary endpoint in the grouped analysis),
- the absence of robust quality of life data versus teriflunomide, in a disease that causes the progressive disability of patients,
- the absence of long-term safety data,

The Transparency Committee considers that KESIMPTA (ofatumumab):
- **provides a moderate clinical added value (CAV III) compared to teriflunomide (AUBAGIO) in patients with early-stage RRMS in terms of disease duration and inflammatory activity,**
- **provides no clinical added value (CAV V) in the care pathway for patients with highly active or severe RMS,**

In the same way as OCREVUS (ocrelizumab).