HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
10 MARCH 2021
The legally binding text is the original French opinion version

apremilast
OTEZLA 10 mg, 20 mg, 30 mg film-coated tablets

New indication

Key points

Favourable opinion for reimbursement in the treatment of adult patients with oral ulcers associated with Behçet's disease (BD), only when colchicine treatment is contraindicated, ineffective or poorly tolerated.

Unfavourable opinion for reimbursement in other situations.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

The medicinal products used in Behçet's disease aim to suppress the inflammatory reaction, treat the main symptoms of the disease and limit complications and damage to the affected organs. The choice of medicinal products depends on the severity and frequency of the symptoms, as well as the organs affected.

Oral ulcers are a very common symptom in Behçet's disease, present in over 90% of cases and usually bipolar, the treatment of which is based on topical treatments containing local anaesthetics, such as lidocaine (viscous solution), chlorhexidine (mouthwash) and corticosteroids (for example clobetasol propionate gel for local application) as first-line therapy. Good oral and dental hygiene is essential.

When systemic treatment is necessary, colchicine is the first-line treatment recommended in the absence of contraindications in order to prevent recurrences of oral or genital ulcers or erythema nodosum lesions, generally at a dosage of between 1 and 2 mg/day. Systemic corticosteroid therapy may be a therapeutic option in recurrent forms and in case of systemic involvement.

In refractory patients, the French national diagnostic and care protocol (PNDS) and EULAR guidelines recommend treatments such as azathioprine, thalidomide (which is the subject of a temporary recommendation for use or RTU), TNF-alpha inhibitors, apremilast or ustekinumab for the treatment of severe cutaneous and mucosal lesions. All these drugs are currently used off-label (excluding apremilast, which now has an MA). In addition, thalidomide is the subject of an RTU in the following indication: "Treatment of severe aphthosis, including in HIV-positive patients and in Behçet's disease, in the event of failure of first-line treatments (local treatments and colchicine)".

Role of the medicinal product in the care pathway

OTEZLA (apremilast) is a second-line treatment for adult patients with oral ulcers associated with Behçet's disease (BD), only when colchicine treatment is contraindicated, ineffective or poorly tolerated.
In addition, considering:

- a modest efficacy demonstrated versus placebo, particularly on the reduction in the number of oral ulcers after 12 weeks of treatment, only in patients with no major organ involvement,
- an improvement in quality of life versus placebo, with difficulties interpreting the clinical relevance of the effect size observed,
- the absence of data versus an active comparator, particularly colchicine,
- the absence of demonstrated efficacy on the other components of this disease (e.g. genital ulcers),

the Transparency Committee considers that the role of OTEZLA (apremilast) in the care pathway for Behçet's disease is limited to the symptomatic treatment of oral ulcers associated with this disease, when colchicine is ineffective, poorly tolerated or contraindicated.
This medicinal product has no role as a first-line treatment in the absence of comparative data with colchicine, which remains the first-line systemic treatment.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Behçet's disease is a rare auto-inflammatory disease, some forms of which can be serious and incapacitating. Cutaneous and mucosal involvement is associated with a marked deterioration in patients' quality of life.

◗ OTEZLA (apremilast) is a symptomatic treatment for the management of ulcers.

◗ Considering:
- a modest efficacy demonstrated versus placebo in a population that for nearly half had previously received colchicine(within 30 days prior to inclusion),
- the absence of comparative data versus colchicine,
- limited follow-up of 12 weeks for efficacy data from the controlled phase and of 16 months for the safety data, with uncertainties concerning the long-term safety, particularly relating to the development of cancers,
- demonstrative quality of life data, although the clinical relevance of the improvement observed is difficult to assess,

the Committee considers that the efficacy/adverse effects ratio of OTEZLA (apremilast) is:
- modest as second-line treatment when colchicine is contraindicated, ineffective or poorly tolerated,
- inadequately established as first-line treatment given the absence of comparative data versus colchicine, which is the standard first-line systemic therapy.

◗ There are alternatives for first and second-line therapy (see Clinically relevant comparators).

◗ OTEZLA (apremilast) is a second-line treatment for adult patients with oral ulcers associated with Behçet's disease (BD), only when colchicine treatment is contraindicated, ineffective or poorly tolerated (see section 08).
In the other situations, particularly for first-line treatment (colchicine eligible patients), OTEZLA has no role in the care pathway, in the absence of comparative data versus colchicine.

Public health impact

Considering:
- the sometimes marked deterioration in patients' quality of life associated with cutaneous and mucosal lesions,
- the low prevalence of the disease (7/100,000),
- the medical need in colchicine-resistant patients partially met by the off-label use of medicinal products in clinical practice,
- the partial response to the identified need as second-line therapy (when colchicine treatment is contraindicated, ineffective or poorly tolerated) taking into account the available study data demonstrating an additional impact compared to placebo in terms of morbidity and quality of life, without, however, any comparative data compared to the existing alternatives (off-label) and the limited experience, particularly in terms of safety,
- the absence of demonstrated impact on the organisation of care (hospitalisation, AEs, etc.),

OTEZLA (apremilast) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of OTEZLA (apremilast) is:
- **moderate only in the treatment of adult patients with oral ulcers associated with Behçet's disease (BD), when colchicine is contraindicated, ineffective or poorly tolerated,**
- **and insufficient to justify public funding cover in view of the available alternatives in other situations.**

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 only in the treatment of adult patients with oral ulcers associated with Behçet's disease (BD), when colchicine is contraindicated, ineffective or poorly tolerated and at the MA dosages and an unfavourable opinion in other situations.

- **Recommended reimbursement rate: 30%**

Clinical Added Value

In the treatment of adult patients with oral ulcers associated with Behçet's disease (BD), when colchicine is contraindicated, ineffective or poorly tolerated

Considering:

- **a modest efficacy demonstrated in two phase 2 and 3 studies versus placebo on the area under the curve for the number of oral ulcers (AUC_{W0-12}), the primary endpoint in the phase 3 BCT-002 study, and on the mean number of oral ulcers at week 12, the primary endpoint in the phase 2 BCT-001 study,**
- **the absence of specific data in patients in whom colchicine is ineffective, poorly tolerated or contraindicated,**
- **the limited follow-up of the controlled treatment phase of the studies (12 weeks) and the absence of long-term safety follow-up,**

OTEZLA proprietary medicinal products provide no clinical added value (CAV V) in the care pathway.