HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
27 OCTOBER 2021

The legally binding text is the original French opinion version

tralokinumab
ADTRALZA 150 mg solution for injection in pre-filled syringe

First assessment

Key points

Favourable opinion for reimbursement in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy **in the event of failure, intolerance, or contraindication to ciclosporin.**

Unfavourable opinion for reimbursement following the failure of topical treatments in **ciclosporin-naive** patients, in the absence of comparative data.

What therapeutic improvement?

No clinical added value in the treatment of adults suffering from moderate to severe atopic dermatitis, requiring systemic treatment, in the event of failure of, intolerance to, or contraindication for ciclosporin.

Role in the care pathway?

The objective of atopic dermatitis treatment is to improve patients' quality of life by treating their skin lesions and preventing the risk of secondary infections in the event of flare-ups, early relapses and xeroderma. Outside inflammatory flare-ups, all patients should be treated using adjuvant measures (hygiene, emollients) and relapses should be treated at an early stage.
The treatment of acute flare-ups is initially based on the use of topical treatments (topical corticosteroids or, in the event of failure/contraindication, a calcineurin inhibitor), which are very effective in the short-term and well tolerated, although treatment compliance could be better given the corticosteroid phobia of patients.
Phototherapy is mainly recommended in the management of the chronic phase but can be used as second-line treatment in acute flare-ups in the event of failure of topical treatments, although its use is limited by its accessibility.

Systemic treatments are reserved for severe chronic atopic dermatitis resistant to topical corticosteroids or phototherapy, with no sufficient data being available to recommend an optimal treatment regimen. The choice of systemic treatment depends on various factors, in particular comorbidities, age, clinical experience or potential pregnancy plans. Non-biologic systemic treatments are currently available, including ciclosporin used as first-line treatment and, in the event of failure, contraindication or intolerance to ciclosporin, dupilumab (IL4 and IL13 inhibitor) and baricitinib (JAK inhibitor) and medicinal products used off-label (methotrexate, mycophenolate mofetil and azathioprine). The use of the latter is based on an insufficient level of scientific evidence and should be time-limited due to their toxicity.
Alitretinoin, a systemic retinoid, has an MA exclusively for the treatment of severe chronic eczema of the hands, following the failure of potent topical corticosteroids.

Role of the medicinal product in the care pathway

As knowledge currently stands, in the absence of a direct comparison of tralokinumab (IL13 inhibitor) with oral ciclosporin following the failure of topical treatments, its role compared to ciclosporin cannot be determined in first-line systemic therapy (following the failure of topical corticosteroids). Consequently, the Transparency Committee considers that ADTRALZA (tralokinumab) is a second-line systemic treatment to be reserved for adults with moderate to severe atopic dermatitis, in the event of failure, intolerance, or contraindication to ciclosporin.

In the absence of comparative data, its role cannot be determined compared to the currently available alternatives, in particular:

- DUPIXENT (dupilumab), another systemic treatment recommended following the failure of ciclosporin, despite this comparison being feasible,

- The JAK inhibitors RINVOQ (upadacitinib) and OLUMIANT (baricitinib), although comparison with these medicinal products was not expected by the Committee given their concomitant development.

Special recommendations

Given the risk of hypersensitivity reactions with tralokinumab administered subcutaneously (see section 4.4 of the SPC), but also with other biologics, the Transparency Committee recommends that the first subcutaneous injection of this medicinal product be given in an appropriate care structure.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Atopic dermatitis is not usually a serious disease but in its moderate to severe forms, it has a significant impact on the quality of life of patients and marked social repercussions.

◗ ADTRALZA 150 mg (tralokinumab) solution for injection in pre-filled syringe has a suspensive effect on symptoms.

◗ In the absence of direct comparison with ciclosporin, the efficacy/adverse effects ratio of ADTRALZA (tralokinumab) has not been established in adults with moderate to severe atopic dermatitis in whom topical treatments have failed and who are ciclosporin-naive. On the basis of available data, its efficacy/adverse effects ratio is high only in patients in whom ciclosporin treatment has failed.

◗ There are medicinal alternatives (see section 5 of this opinion).

◗ This medicinal product is a second-line systemic treatment to be reserved for adults with moderate to severe atopic dermatitis, in the event of failure, intolerance, or contraindication to ciclosporin. There is no available comparative data versus DUPIXENT (dupilumab) despite this being feasible, nor versus the JAK inhibitors RINVOQ (upadacitinib) and OLUMIANT (baricitinib), which were developed concomitantly, meaning that the role of ADTRALZA (tralokinumab) compared to these medicinal products cannot be determined (see section 09 role in the care pathway).

Public health impact

Considering:

- the seriousness of the disease in its severe forms requiring systemic treatment and its significant impact on patients' quality of life,
- the high prevalence of the disease (between 2 and 5% of the adult population),
- the medical need that is partially met in adults with moderate to severe atopic dermatitis who are candidates for systemic therapy,
- the partial response to the identified need, due to:
    - an impact in terms of morbidity (IGA 0 or 1 and EASI-75 responses) demonstrated only versus placebo,
    - a non-clinically relevant impact demonstrated versus placebo in terms of quality of life in patients with no prior ciclosporin treatment failure and the absence of a demonstrated impact on this endpoint in patients following failure of ciclosporin treatment,
    - the lack of demonstrated impact on the patient's care or life pathway,

ADTRALZA (tralokinumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ADTRALZA 150 mg (tralokinumab) solution for injection in pre-filled syringe is:

- **substantial only in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy, in the event of failure, intolerance, or contraindication to ciclosporin.**
- **insufficient to justify public funding cover in ciclosporin-naive patients in view of the available alternatives.**

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 moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin and at the MA dosages.

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 treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy and who are ciclosporin-naive.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

- **Within the reimbursement scope retained by the Committee**

Considering:

- demonstration of the superiority of tralokinumab compared to placebo in terms of IGA 0 or 1 and/or EASI-75 responses after 16 weeks of treatment (primary endpoints depending on the studies):
    - as monotherapy (ECZTRA 1 and 2 studies) or in combination with topical corticosteroids (ECZTRA 3 study), in adults with moderate to severe atopic dermatitis who are candidates for systemic therapy,
    - in patients with failure (inadequate response, intolerance or contraindication) of ciclosporin (ECZTRA 7 study),
- a safety profile mainly marked by upper airway infections, injection site reactions and conjunctivitis,

But considering:

- the statistically significant, but not clinically relevant, differences observed versus placebo in terms of quality of life (DLQI) in patients who are candidates for systemic therapy (ECZTRA 1, 2 and 3 studies) and the absence of demonstration of the superiority of tralokinumab compared to placebo for this score in patients in whom ciclosporin treatment has failed (ECZTRA 7 study, discontinuation of the hierarchical sequence meaning that it was not possible assess this endpoint),
- uncertainties with respect to maintenance of efficacy beyond 52 weeks of treatment
- the absence of a comparison with dupilumab following the failure of ciclosporin, whereas this could have been performed,

ADTRALZA 150 mg (tralokinumab) solution for injection in pre-filled syringe provides no clinical added value (CAV V) in the care pathway for moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin.