HAUTE AUTORITÉ DE SANTÉ

DERMATOLOGY
New medicinal product
July 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

DUPIXENT (dupilumab), non-corticosteroid dermatitis medicine

High clinical benefit in the treatment of moderate to severe atopic dermatitis (AD) in adults, requiring systemic treatment, only in the event of failure, intolerance or contraindication to cyclosporine and moderate therapeutic progress in the therapeutic strategy

Insufficient clinical benefit to justify its reimbursement for moderate to severe atopic dermatitis in adults, following failure of topical treatments and in systemic treatment-naive patients, failing any robust comparative data *versus* oral cyclosporine

Main points

- DUPIXENT has been granted marketing authorisation for the treatment of moderate to severe atopic dermatitis (AD) in adults, requiring systemic treatment.
- It has high clinical benefit only as second-line treatment after cyclosporine failure, intolerance or contraindication.
- In systemic treatment-naive patients, its clinical benefit is insufficient, failing robust comparative data *versus* cyclosporine.

Therapeutic strategy

- The treatment of mild to moderate AD is based on the use of topical corticosteroids (TCS), that are tapered gradually once symptoms improve and the potency of which should be selected according to disease severity, safety and lesion site. Topical treatment may be reinforced by “wet wrapping”. If no improvement is achieved, despite correctly administered TCS treatment, or in the event of TCS intolerance (risk of atrophoderma), topical tacrolimus (PROTOPIC) may be used, preferably on small, resistant lesions, mainly on the neck, face, genital area and skin folds. Its use is time-limited (2 weeks) due to the risk of lymphoma.
- Phototherapy (UVB 311 nm, PUVA or UVA1) is second-line treatment, following failure of, or intolerance to topical treatments, or as adjuvant treatment prior to initiation of systemic treatment. Its role is not clearly defined and its use is limited by accessibility and by long-term carcinogenic risk (in particular for PUVA therapy).
- In the event of severe AD, or lack of response to first-line treatments, systemic treatment may be prescribed. Oral cyclosporine, which is the only drug to have been granted marketing authorisation in this indication, is used as a first-line treatment. It is rapidly effective against lesions and pruritus, though its use rarely exceeds 1 year due to its long-term safety profile (renal toxicity in particular).
- Methotrexate, used off-label, is a preferred alternative to cyclosporine, even though its time to onset of action is longer and its safety marked by gastrointestinal disorders, myelotoxicity and hepatotoxicity limits its use. The off-label use of azathioprine is marginal due to its poor long-term safety. Systemic corticosteroids are rarely used and should be avoided. Alitretinoin, a systemic retinoid, has been granted marketing authorisation exclusively for the treatment of severe chronic hand eczema, after failure of potent topical corticosteroids

- **Role of the medicinal product in the therapeutic strategy**
  DUPIXENT is a second-line systemic treatment to be reserved for adults suffering from moderate to severe AD, following cyclosporine failure, intolerance or contraindication.
  In the absence of direct comparison of DUPIXENT to cyclosporine, whereas this comparison could have been performed, the role of DUPIXENT relative to oral cyclosporine after failure of topical treatments cannot be established.

Clinical data

- The efficacy of dupilumab (1 x 600 mg injection, followed by 300 mg every 2 weeks) combined with a TCS, was evaluated versus placebo + TCS in 325 adults suffering from severe AD, following failure of, or intolerance to cyclosporine, or for whom cyclosporine was not appropriate. The dupilumab + TCS combination was superior to placebo + TCS over the fraction of EASI-75 responders at W16 (primary endpoint), with 62.6% responders *versus* 29.6% ($p < 0.0001$).
- Three other studies were conducted in the population covered by the MA, i.e. in patients suffering from moderate to severe AD, requiring systemic treatment (failure of topical treatments). *Post-hoc* analyses of these studies suggest the superiority of dupilumab over the placebo in subgroups of patients previously treated, or not, with systemic immunosuppressors (in particular cyclosporine), and in the subgroup of patients for whom cyclosporine was inappropriate (failure, intolerance, contraindication or advised against), or who had previously received methotrexate or azathioprine.
- The main adverse events associated with dupilumab were rhinopharyngitis, injection site reactions, allergic conjunctivitis, blepharitis, along with herpes infections and transient hypereosinophilia. Serious adverse events with dupilumab occurred in around 1 to 4% of cases and fewer than 1% required treatment discontinuation. Anti-dupilumab antibodies were observed in 5 to 6% of patients, though no difference in efficacy was noted according to the presence or absence of these antibodies.

Special prescription requirements

- Medicinal product subject to initial annual hospital prescription
- Initial prescription and renewal reserved for dermatology or internal medicine specialists.

Benefit of the medicinal product

- The actual clinical benefit* of DUPIXENT is:
  - high 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 cyclosporine.
  - insufficient to justify public funding cover for adults suffering from moderate to severe atopic dermatitis, following failure of topical treatments and systemic treatment-naive, failing robust comparative data *versus* oral cyclosporine.
- DUPIXENT provides moderate clinical added value** (CAV III) in the therapeutic strategy
- Approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated AA July 2018 (CT-16605) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) is its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"