HAUTE AUTORITÉ DE SANTÉ

OPHTHALMOLOGY
New indication
June 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

HUMIRA (adalimumab), anti-TNFα immunosuppressant

In combination with methotrexate, moderate clinical benefit and minor clinical improvement in the treatment of non-infectious chronic anterior uveitis associated with juvenile idiopathic arthritis in children (2 to 17 years), in cases of insufficient response or intolerance to conventional treatment or for whom conventional treatment is unsuitable.

Main points

- HUMIRA has MA for the treatment of non-infectious chronic anterior uveitis in children from 2 years and adolescents in cases of insufficient response or intolerance to conventional treatment or for whom conventional treatment is unsuitable.
- Its efficacy has been demonstrated versus placebo in a restricted MA population, in patients with uveitis associated with juvenile idiopathic uveitis after corticosteroid failure and in combination with methotrexate
- The clinical improvement is minor, particularly due to uncertainties in respect of the effect size due to the methodological bias and weaknesses of the studies and the lack of long-term data.

Pre-existing indications*

HUMIRA proprietary medicinal products have other indications: in uveitis in adults, rheumatology, gastroenterology and dermatology (see details of indications in SPC).

Therapeutic strategy

- The treatment of uveitis, in particular non-infectious chronic anterior uveitis associated with juvenile idiopathic arthritis, involves, as a first-line approach, corticotherapy administered topically or by the systemic route in the event of a high sight-threatening risk. A conventional immunosuppressant treatment (methotrexate, azathioprine, ciclosporin, etc.) may be initiated after corticosteroid treatment failure, or in the event of intolerance. These medicinal products are used off-label in this indication.
  After corticotherapy and immunosuppressant treatment failure or intolerance, the anti-TNFα agents, adalimumab or infliximab, are generally used.
- **Role of the medicinal product in the therapeutic strategy**

  HUMIRA is a third-line treatment, in combination with methotrexate and with corticosteroids, for children from 2 years and adolescents with non-infectious chronic anterior uveitis, associated with juvenile idiopathic arthritis, in cases of insufficient response or intolerance to conventional treatment or for whom conventional treatment is unsuitable.

  Failing specific clinical data, HUMIRA has no role in the therapeutic strategy in other cases of non-infectious chronic anterior uveitis.

Clinical data

* This summary does not concern these indications.

- Adalimumab was assessed in 2 double-blind, randomised, placebo-controlled studies on patients aged from 2 to 17 years with active uveitis associated with juvenile idiopathic arthritis and after failure of local corticotherapy and methotrexate (0.3 to 0.6 mg/kg, not exceeding 25 mg) once a week for at least 3 months. During the studies, the corticosteroid (topical or systemic) and methotrexate treatments were retained.
  A first study scheduled to be conducted over 18 months and to include 114 patients was terminated early following the findings of the second intermediate analysis envisaged in the protocol concerning 90 patients (2:1 randomisation). The median treatment exposure time was 87 days in the placebo group and 353 days in the adalimumab group. A large number of major breaches of the protocol were observed. The primary endpoint was the time to onset of relapse, a composite endpoint accounting for:
  - the inflammatory score of the anterior segment (Tyndall score) after at least 3 months of treatment and/or
  - the use of concomitant treatments and/or
  - the intermittent or continuous discontinuation of the study treatment (adalimumab/placebo) over a cumulative period of more than 4 weeks.

  The median time to onset of relapse was longer with adalimumab than with the placebo ($p < 0.001$). It was 24.1 weeks in the placebo group and could not be estimated in the adalimumab due to the low number of relapsed subjects in this group. The percentage of relapsed patients was 26.7% in the adalimumab group and 60% in the placebo group ($p < 0.0001$).
  The second study demonstrated the superiority of adalimumab over the placebo in terms of the percentage of patients responding to the treatment defined by a reduction in the Tyndall score ≥ 30% and no worsening under slit-lamp examination (56% versus 20%, $p = 0.038$). This study has a lower level of evidence due to the low number of patients included (n = 32) and a short-term assessment (2 months).
- The safety profile of adalimumab in patients with uveitis is similar to that observed in other indications.

Special prescription requirements

- Initial annual hospital prescription.
- Prescription by rheumatology, paediatrics, internal medicine, gastroenterology and hepatology, dermatology or ophthalmology specialists.

Benefit of the medicinal product

- The actual clinical benefit* of HUMIRA is moderate in its new indication.
- HUMIRA provides a minor improvement in actual clinical benefit** (IACB IV) in the treatment of these patients.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 13 June 2018 (CT-16820) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of 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 improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"