HAUTE AUTORITÉ DE SANTÉ

RHEUMATOLOGY
Focus
June 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

HUMIRA (adalimumab) **and ENBREL** (etanercept), anti-TNF

Second-line treatments in juvenile idiopathic arthritis (JIA) in case of insufficient response or intolerance to methotrexate.

Main points

- Two anti-TNFs, HUMIRA and ENBREL, which have Marketing Authorisation as a first-line treatment for the active polyarticular form of JIA now have Marketing Authorisation in other forms of the disease:
  - the enthesitis-related form, from 6 years of age for HUMIRA and from 12 years of age for ENBREL.
  - psoriatic arthritis from 6 years of age and extended oligoarthritis from 2 years of age, for ENBREL only.
- These are second-line treatments, prescribed in case of insufficient response or intolerance to methotrexate, reference long-term first line treatment.

Therapeutic use

- The treatment of JIA uses immediately-acting symptomatic treatments (NSAIDs, combined if necessary with intra-articular infiltrations of corticosteroids) and sometimes first-line treatment (methotrexate and biological treatments).
- In the active polyarticular forms without systemic signs, the first line long-term treatment is methotrexate (MTX). Leflunomide, hydroxychloroquine, sulfasalazine, azathioprine and cyclosporine are sometimes used off-label as an alternative to methotrexate. If first-line long-term treatment fails, two anti-TNFs, adalimumab and etanercept, have Marketing Authorisation in children from 2 years of age.
  In patients having had an insufficient response to one of these two anti-TNFs, the alternatives are the addition of MTX if the anti-TNF was used as monotherapy or use of the anti-TNF which has not yet been used or even, in children aged 6 years and over, abatacept (ORENCIA) or tolicilzumab from 2 years of age.
  In the juvenile extended oligoarthritis form, two biological treatments have Marketing Authorisation from 2 years of age, in case of inadequate response or proven intolerance to methotrexate:
  - ENBREL (etanercept), anti-TNF
  - ROACTEMRA (tocilizumab), anti-IL-6
- In the enthesitis-related form, two anti-TNFs, adalimumab and etanercept, have Marketing Authorisation in case of insufficient response or intolerance to standard treatment:
  - ENBREL (etanercept): in adolescents aged 12 years or over
  - HUMIRA (adalimumab): in children and adolescents aged 6 years or over.
- In psoriatic arthritis, ENBREL is the only biological treatment with Marketing Authorisation in this indication from 12 years of age.

- **Role of anti-TNFs in the therapeutic strategy**
  In the treatment of JIA, ENBREL and HUMIRA are second-line long-term treatments, in case of insufficient response to one or more long-term treatments.
  Generally, in the absence of a study versus active comparator, the role of HUMIRA or ENBREL in the therapeutic strategy for the various categories of JIA for which they have Marketing Authorisation is difficult to establish.

Clinical data

- For ENBREL, the efficacy data in the three new categories of JIA are very limited because they are from an open-label study, with a low level of evidence, during which 60 patients aged 2 to 17 years with extended oligoarthritis and 67 patients aged 12 to 17 years with enthesitis-related JIA or psoriatic arthritis were treated for 12 weeks.
  The ACR paediatric 30 response rate at week 12 (primary endpoint) was 88.6%, 95%CI [81.6; 93.6] for the three types of JIA together (89.7% [78.8; 96.1] in those with extended oligoarthritis, 93.1% [77.2; 99.2] for psoriatic arthritis and 83.3% [67.2; 93.6] for enthesitis-related JIA).
  Its efficacy has not been studied in patients aged less than 12 years in enthesitis-related JIA and psoriatic arthritis and in patients aged less than 2 years in extended oligoarthritis.

- For HUMIRA, the extension of the Marketing Authorisation in enthesitis-related JIA is based on a randomised double blind placebo-controlled study for 12 weeks, followed by an open-label extension phase having included 46 patients aged 6 to 17 years. A mean reduction of -62.6% was observed in patients treated with HUMIRA compared with -11.6% in patients receiving the placebo, p = 0.039 in relation to the primary efficacy endpoint which was the percentage variation of the number of active joints affected by arthritis between inclusion and week 12. Per protocol analysis of sensitivity did not confirm the intention-to-treat analysis result. No statistically significant difference was observed for the secondary endpoints such as the response according to the ACR paediatric criteria.
  It has not been studied in patients below the age of 6 years in enthesitis-related JIA.

- For these two medicinal products, the safety results, definitely limited, did not reveal any new adverse event.

Special prescribing conditions

Exception drug status
Initial annual hospital prescription
HUMIRA: prescription restricted to specialists in rheumatology, gastroenterology and hepatology, gastrointestinal surgery, dermatology, paediatrics and internal medicine
ENBREL: initial and repeat prescription reserved for specialists in rheumatology, internal medicine, paediatrics or dermatology.

Benefit of the medicinal product

- In the treatment of polyarticular juvenile idiopathic arthritis, the actual benefit* of ENBREL and HUMIRA is significant.
- In the treatment of extended oligoarthritis, enthesitis-related JIA and psoriatic arthritis, the actual benefit* of ENBREL is moderate.
- In the treatment of enthesitis-related JIA, the actual benefit* of HUMIRA is significant.
- These proprietary medicinal products do not provide clinical added value** (CAV V) in the management of patients.
- Recommends continued inclusion on the list of reimbursable products for hospital use and supply by pharmacists.

HAS
HAUTE AUTORITÉ DE SANTÉ
This document was created on the basis of the Transparency Committee Opinion of 01 April and 17 June 2015 (CT-14088 and CT-14261) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".