HAUTE AUTORITÉ DE SANTÉ

RHEUMATOLOGY
New indication
December 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

XELJANZ (tofacitinib), anti-JAK 1 and 3

Moderate clinical benefit in psoriatic arthritis but no demonstrated clinical added value in the therapeutic strategy

Main points

- XELJANZ has a marketing authorisation in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. It is administered orally, twice daily.
- Its efficacy has been demonstrated compared to placebo on ACR 20 and functional disability index score (HAQ-DI) in TNF inhibitor-naive patients and in patients having had an inadequate response to at least one TNF inhibitor.
- Its effect on the progression of joint destruction has not been demonstrated.
- It has not been compared to TNF inhibitors, whereas this comparison was possible.
- There are concerns with respect to its long-term safety, particularly as concerns infectious, cardiovascular and carcinogenic risks.

Therapeutic strategy

- The management of psoriatic arthritis combines symptomatic treatment (NSAIDs, with or without analgesics) with disease-modifying antirheumatic drug (DMARD) therapy. For the latter, a distinction is made between standard treatment, i.e., methotrexate, leflunomide and sulfasalazine (off-label), and, if these fail or are contraindicated or not tolerated, TNF inhibitors, IL-23 inhibitors and IL-17 inhibitors.
- The five TNF inhibitors currently available – adalimumab, etanercept, infliximab, golimumab and certolizumab pegol – have marketing authorisations in the treatment of psoriatic arthritis. In the absence of any direct comparison data, no information is available enabling these to be ranked in order. If treatment with a TNF inhibitor fails, the use of another TNF inhibitor should be envisaged.
  Among the various interleukin inhibitors, ustekinumab, an IL-12 and 23 inhibitor, only has a marketing authorisation in the event of failure of nonbiological DMARD therapy, and two IL-17 A inhibitors – secukinumab and ixekizumab – have a marketing authorisation in the event of failure of DMARD therapy.
  When biological therapy is not envisaged, apremilast (OTELZA), an oral phosphodiesterase 4 inhibitor, may be used.
- **Role of the proprietary medicinal product in the therapeutic strategy**
  Considering:
  - experience of around 15 years with TNF inhibitors (marketing authorisation for etanercept dating back to 2003),
  - the demonstration of clinical efficacy on peripheral and axial damage and joint destruction with this class of medicines, which is not the case for XELJANZ,
  - the absence of any direct comparison between tofacitinib and TNF inhibitors,

  in the event of failure of standard DMARD therapy, TNF inhibitors should be favoured as a first-line treatment. XELJANZ primarily has a role following the failure of at least one TNF inhibitor.
  In the absence of any comparison between tofacitinib and the other treatment options available following the failure of at least one TNF inhibitor, i.e., IL-17 inhibitors (ixekizumab and secukinumab) and IL-12 and 23 inhibitors (lustekinumab), its role compared to these medicinal products cannot be specified.

Clinical data

- Tofacitinib (XELJANZ) was assessed in two double-blind, randomised, placebo-controlled studies, one in biological treatment-naive patients (with an adalimumab group but with no scheduled comparison) and the other in patients having had an inadequate response to at least one TNF inhibitor.
- The superiority of tofacitinib 5 mg twice daily compared to placebo was demonstrated on the basis of criteria assessing the signs, symptoms and physical function of PsA after 3 months:
  - in TNF inhibitor-naive patients, the absolute benefit in terms of ACR20 response was 17% in favour of tofacitinib and 0.35 points in terms of HAQ-DI;
  - in patients having had an inadequate response to a TNF inhibitor, the absolute benefit in terms of ACR20 response was 26% in favour of tofacitinib and 0.39 points in terms of HAQ-DI.

  Its effect on the inhibition of radiographic progression was not demonstrated.
- Uncertainties and concerns remain with respect to the long-term safety of tofacitinib, particularly in terms of the carcinogenic and cardiovascular risk.

Special prescription requirements

- Medicinal product subject to initial annual hospital prescription
- Initial prescription and renewal reserved for rheumatology, dermatology or hepato-gastroenterology specialists.

Benefit of the medicinal product

- The actual clinical benefit* of XELJANZ is moderate.
- XELJANZ does not provide any clinical added value** (CAV V) in the treatment strategy for active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARD).
- Approved for non-hospital pharmacy reimbursement and for hospital treatment within this indication.

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This document was drafted on the basis of the Transparency Committee opinion dated 05 December 2018 (CT-17188)
available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

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