HAUTE AUTORITÉ DE SANTÉ

RHEUMATOLOGY
New medicinal product
September 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

XELJANZ (tofacitinib), anti-JAK 1 and 3

No clinical benefit demonstrated in the treatment of rheumatoid arthritis (RA) after failure of one or more disease-modifying antirheumatic drugs (DMARD)

Main points

- XELJANZ has a Marketing Authorisation in the treatment of rheumatoid arthritis (RA) after failure of one or more DMARDs. It is administered orally, twice a day.
- It is a second-line treatment after failure of conventional DMARDs such as methotrexate (MTX), as a third-line treatment (after failure of a biological DMARD) or beyond (failure of multiple conventional and/or biological DMARDs).
- Its non-inferiority has been demonstrated in combination with MTX compared with adalimumab in second-line (after MTX failure); its superiority has not been demonstrated. XELJANZ has not been compared to available third-line alternatives (in particular tocilizumab, abatacept, rituximab).
- There are concerns in terms of long-term safety, in particular in relation to risks of infection and cardiovascular and carcinogenic risks.

Therapeutic strategy

- RA treatment relies on the early prescription (earliness is a determining factor in the success of the treatment) of a DMARD to induce clinical and laboratory remission. The standard conventional DMARD remains methotrexate. Different DMARDs need to be available because of treatment resistance, treatment failure or intolerance, as well as the need for multiple drug presentations.
- **Role of the proprietary medicinal product in the therapeutic strategy**
  Considering, on the one hand, the concerns in terms of safety (especially long-term) related to this new mechanism of action and, on the other hand, the greater experience with biological medicinal products in terms of efficacy and safety, the Committee recommends that XELJANZ be used preferably in third-line (namely, after failure of a biotherapy) or beyond. Preference must be given to its combination with MTX over monotherapy which should be reserved for situations of intolerance to MTX or when continued treatment with MTX is inappropriate.

Clinical data

- The efficacy of tofacitinib in the treatment of RA has been evaluated in seven randomised double-blind controlled trials. Several populations have been studied: methotrexate-naïve patients or after failure of a DMARD (second-line or beyond).
- In combination with MTX or another conventional DMARD, the superiority of tofacitinib has been demonstrated compared to placebo + MTX or another conventional disease-modifying treatment in four of the trials.
- In monotherapy, the superiority of tofacitinib has been demonstrated in two trials (in MTX-naïve patients and in patients after failure of at least one DMARD).
- Inhibition of radiographic progression was evaluated as a co-primary efficacy endpoint in two trials. In the trial conducted in MTX-naïve patients, the superiority of tofacitinib 5 mg/day (Marketing Authorisation dose) in monotherapy versus MTX was demonstrated: difference of 0.7 [-1.0; -0.3] at 6 months on the van der Heijde-modified Total Sharp Score (mTSS). However, in the study conducted in MTX failure, significance was not achieved for tofacitinib + MTX versus placebo + MTX.
- In patients who failed MTX, only the non-inferiority of tofacitinib 5 mg twice a day in combination with MTX compared with adalimumab 40 mg/day in combination with MTX was demonstrated. Superiority was not demonstrated.

- The non-inferiority of tofacitinib in monotherapy compared with tofacitinib in combination with MTX has not been demonstrated.
- There are doubts and concerns about the long-term safety of tofacitinib, particularly concerning the carcinogenic and cardiovascular risk.

Special prescribing conditions

- Medicinal product for initial annual hospital prescription.
- Initial prescription and renewal by rheumatology specialists only.

Benefit of the medicinal product

- The actual clinical benefit* of XELJANZ is substantial.
- XELJANZ does not provide any clinical added value** (CAV V) in the management of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response, or intolerance, to one or more DMARDs.
- Inclusion on the list of reimbursable products for supply by pharmacists and for hospital use Recommended.

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This document was created on the basis of the Transparency Committee Opinion of 27 September 2017 (CT-16198) and is 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 can be substantial, moderate, low or insufficient for reimbursement of the medicinal product 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 (equivalent to “no CAV”) means “no clinical added value”.