HAUTE AUTORITÉ DE SANTÉ

GASTROENTEROLOGY
New indication
March 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

XELJANZ (tofacitinib), janus kinase inhibitor

High clinical benefit and minor clinical improvement in patients suffering from moderate to severe active ulcerative colitis for whom conventional and anti-TNF treatment has failed.

Insufficient clinical benefit to justify its reimbursement in patients for whom conventional treatment has failed and who have never received an anti-TNF.

Main points

- XELJANZ has been granted a marketing authorisation for the treatment of moderate to severe active ulcerative colitis (UC) in adults having presented an inadequate response, loss of response or intolerance, either to the conventional treatment, or to a biological agent.
- As a third-line treatment, in patients for whom conventional and anti-TNF treatment has failed, it represents an alternative to ENTYVIO (vedolizumab). The choice is made, in agreement with the patient and their preferences, taking into consideration the various administration conditions of these two medicinal products and their safety profiles.
- Failing any direct comparison with an anti-TNF, XELJANZ has not established its role as a second-line treatment. The medical need is covered by anti-TNF products.
- Tofacitinib has no role in the medical-surgical management of patients suffering from severe colitis.

Pre-existing indications*

- XELJANZ has already been granted a marketing authorisation for the treatment of psoriatic arthritis and rheumatoid arthritis (for further details, see SPC).

Therapeutic strategy

- Once remission has been induced, the aims of the medical treatment are to maintain this remission without corticosteroids and to improve the patient's quality of life. The choice of treatment is governed, in particular, by the severity of the disease and the extent of colon damage. As second-line treatment of moderate to severe active UC in adults who responded inadequately to the conventional treatment, or for whom this treatment is contraindicated or poorly tolerates, anti-TNF medicinal products (infliximab, adalimumab and golimumab) are the reference treatment. As third-line treatment, in patients for whom conventional and anti-TNF treatment has failed, ENTYVIO (vedolizumab) is the only alternative.
- Surgical treatment is considered primarily in cases of incapacitating UC refractory to medicinal products, or in the event of severe acute complications (haemorrhage, perforation or toxic megacolon).
- **Role of the medicinal product in the therapeutic strategy**
  - As third-line treatment, XELJANZ is an alternative to vedolizumab. The choice is made, in agreement with the patient and their preferences, taking into consideration the various administration conditions of these two medicinal products and their safety profiles (tofacitinib: oral, twice daily with need for regular biological monitoring; vedolizumab: parenteral by IV infusion, followed by additional infusions at 2 and 6 weeks, then every 8 weeks).

* This summary does not concern these indications.

- The role of XELJANZ as second-line treatment, in the event of failure of conventional treatment and for patients who have never received an anti-TNF medicinal product, has not been established.

Clinical data

- **For induction of remission**: two phase III randomised, double-blind studies, OCTAVE 1 and 2, compared tofacitinib 10 mg x 2/day to placebo according to a similar methodology. These studies randomised 1,139 patients, 905 of whom were placed in the tofacitinib group and 234 in the placebo group. In the 1st study, 80.6% of all patients were failing 5-aminosalicylates, 74.9% were failing corticosteroids, 74.1% were failing an immunosuppressor and 51.3% were failing an anti-TNF medicinal product. In the second study, 71.9% of all patients were failing 5-aminosalicylates, 71.3% were failing corticosteroids, 69.5% were failing an immunosuppressor and 52.1% were failing an anti-TNF medicinal product. After 8 weeks of treatment, the proportion of patients in remission (primary endpoint) was higher in the tofacitinib groups than in the placebo group, with a difference in favour of tofacitinib of 10.3% (CI95% [4.3; 16.3], p=0.0070) in the first study and of 13% (CI95% [8.1; 17.9], p=0.0005) in the second study. The proportion of patients with mucosal healing (ranked secondary endpoint) was higher in the tofacitinib group than in the placebo group.
- **For maintenance of remission**: the patients included in the induction studies and who demonstrated a clinical response (secondary endpoint) at week 8, were included in the OCTAVE Sustain phase III randomised, double-blind study that compared tofacitinib to the placebo. The study randomised 593 patients, of whom 198 were placed in the tofacitinib 5 mg x 2/day group, 197 in the tofacitinib 10 mg x 2/day group and 198 in the placebo group. Of these, 179 patients were in remission upon inclusion. After 52 weeks of treatment, the proportion of patients in remission (primary endpoint) was higher in the tofacitinib group (34.3%) than in the placebo group (11.1%), with a difference of 23.2% (CI95% [15.3; 31.2], p<0.0001). This percentage was higher in the tofacitinib 10 mg group (40.6%) than in the placebo group (11.1%), i.e. a 29.5% difference (CI95% [21.4; 37.6], p<0.0001). The superiority of tofacitinib at these two dosages over the placebo was also demonstrated for the secondary endpoints “mucosal healing at week 52” and “proportion of patients in prolonged remission without corticosteroids among patients in remission upon inclusion, at weeks 24 and 52”, considering that both of these endpoints were analysed with an appropriate alpha risk management method.
- **Tofacitinib safety** was similar to that observed in rheumatoid arthritis. Usage perspective remains weak and long-term data are limited. The risk management plan stipulates the monitoring of several major risks: infections, hypersensitivity reactions and neutropenia, digestive inflammatory diseases such as Crohn’s disease and ulcerative colitis, major cerebral/cardiovascular events and cancer.

Special prescription requirements

- Medicinal product subject to initial annual hospital prescription. Initial prescription and renewals reserved for hepato-gastroenterology specialists.
- Exception drug

Benefit of the medicinal product

- The actual clinical benefit* of XELJANZ is high in patients failing (insufficient response, loss of response or intolerance) conventional treatment (5-aminosalicylates, corticosteroids and immunosuppressors) and anti-TNF medicinal products.
- The actual clinical benefit of XELJANZ is insufficient to justify public funding cover for patients with inadequate response, loss of response or intolerance to the conventional treatment (i.e. anti-TNF treatment-naive patients).
- XELJANZ provides a minor clinical added value** (CAV IV) in patients suffering from moderate to severe active ulcerative colitis for whom conventional and anti-TNF treatment has failed.
- Approval for non-hospital pharmacy reimbursement and for hospital treatment, exclusively for patients failing conventional treatment (5-aminosalicylates, corticosteroids and immunosuppressors) and anti-TNF medicinal products.

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This document was drafted on the basis of the Transparency Committee opinion dated 20 March 2019 (CT17198 and 17229) 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".