Conitec

Recomendation report

DRUGS

Nº 538
June/2020

Tofacitinib citrate for the treatment of moderate to severe ulcerative colitis in adult patients with inadequate response, loss of response or intolerance to previous treatment with conventional synthetic or biological drugs

Brasília – DF
2020

Technology: Tofacitinib Citrate (Xeljanz®).

Indication: Induction or maintenance treatment of moderately to severely active ulcerative colitis in adult patients with inadequate response, loss of response or intolerance to corticosteroids, azathioprine (AZA), 6-mercaptopurine (6-MP) or Tumour Necrosis Factor (TNF) antagonists.

Applicant: Pfizer.

Background: Ulcerative Colitis (UC) is a chronic disease characterized by the inflammation of the mucosal layer of the colon, which affects the rectum and the colon proximal. It is often accompanied by diarrhoea (bloody or not), together with small and frequent bowel movements. Other symptoms include clinical manifestations, such as fever, weight loss, anaemia, abdominal pain, and laboratory changes. UC can be classified by severity as mild, moderate or severe, which helps determine treatment, based on the application of an index. The treatment currently recommended in the Brazilian Public Health System (SUS) is the use of corticosteroids and aminosalicylates.

Question: Is tofacitinib citrate effective and safe for the treatment of moderately to severely active UC in adult patients with inadequate response, loss of response or intolerance to aminosalicylates, corticosteroids, azathioprine, 6-mercaptopurine or anti-TNF biologic drugs?

Scientific evidence: The applicant presented six scientific studies and one meta-analysis of indirect comparison (own elaboration). Conitec's Executive Secretariat also conducted a search and included another indirect comparison study. In conclusion, the following studies were analysed: 1 study of 3 clinical trials (Sandborn, 2017), assessed with low risk of bias; 2 systematic reviews with indirect comparisons (Bonovas, 2018, and Trigo-Vicente, 2018); and 2 studies of post-hoc analysis of quality of life (Panés, 2017) and safety (Sandborn, 2018). These studies had a moderate quality score, according to a specific tool. In individuals with moderate to severe ulcerative colitis, therapy with tofacitinib at a dose of 10 mg twice daily for 8 weeks was associated with clinical remission in a higher, and statistically significant, proportion of patients compared with placebo, from 10% (95% Confidence Interval [CI] 4.3-16.3) to 13% (95% CI 8.1-17.9). In the maintenance phase (52 weeks), therapy with tofacitinib at a dose of 5 mg and 10 mg twice daily was also associated with a greater clinical remission compared with placebo (difference of 23.2% [95% CI 15.3-31.2%] and 29.5% [95% CI 21.4-37.6%], respectively). In relation to the mucosal healing outcome, therapy with tofacitinib at a dose of 5 mg and 10 mg for 8 weeks was associated with a higher percentage of cure compared with placebo (15.7% [p<0.001] and 16.8% [p<0.001], respectively). This difference remained statistically significant at week 52 (24.2 [p <0.001] and 32.6 [p <0.001], respectively). Sustained corticosteroid-free remission was achieved in 35.4% in the tofacitinib 5 mg group, 47.3% in the tofacitinib 10 mg group, and 5.1% in the placebo group, with a statistically significant difference. The use of tofacitinib was associated with an improvement in quality of life. As for the indirect comparison studies, therapy with infliximab and vedolizumab showed better results in the evaluated outcomes compared with other biologics, or they were not considered different from tofacitinib for the outcome of clinical remission at week 8. Regarding safety, tofacitinib seemed similar to placebo in the induction phase for more common adverse events such as nasopharyngitis, arthralgia and headache. However, the studies also reported serious infections (appendicitis, anal abscess), opportunistic infections (herpes zoster, clostridium difficile), gastrointestinal perforation, cardiovascular events, and cancer.

Economic evaluation: The applicant submitted a Cost-Minimization Analysis (CMA), based on the assumption that tofacitinib is not different from biologics. In general, this CMA had few limitations related to calculation of the ampoules of infliximab, dosage form of a comparator (golimumab), and not considering administration costs. It showed that the cost of therapy with infliximab and vedolizumab, compared with tofacitinib, was estimated to be 35% and 67% higher, respectively, in the first year, and 25% and 61% higher in the following years.

However, after analysing the scientific evidence, it was considered that the cost-effectiveness analysis would have been the most appropriate economic evaluation.

Budget impact analysis: A range of scenarios was presented varying comparators and market shares. Two scenarios compared tofacitinib, infliximab and vedolizumab, with different market shares. In the scenario with a greater participation of infliximab, the impact of including tofacitinib would result in savings of BRL 10.1 million in the first year and BRL 95.6 million in five years. In the scenario with a greater participation of vedolizumab, the savings would be of BRL 12.73 million in the first year and BRL 124.24 million in five years. As the population estimated by the applicant was different from Conitec's recent report on treatment of UC, scenarios considering this population were also included.

International recommendations: The National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), and Scottish Medicines Consortium (SMC) recommend tofacitinib for the treatment of moderately to severely active UC in adults when conventional therapy (aminosalicylates, corticosteroids or thiopurines) or a biological agent (infliximab, adalimumab and golimumab or vedolizumab) cannot be tolerated, or if the disease has responded inadequately or lost response to treatment.

Technology horizon scanning: Structured searches were carried out on ClinicalTrials.gov and Cortellis™, in order to identify potential drugs for the treatment of moderate to severe UC in patients with inadequate response, loss of response or intolerance to corticosteroids, azathioprine, mercaptopurine or anti-TNF. Eleven potential drugs were identified.

Considerations: The scientific evidence consisted of Randomized Controlled Trials (RCTs) and indirect comparisons of high to moderate quality, despite the limitations. The RCTs evaluated tofacitinib only in comparison with placebo, that is, no head-to-head comparison was found. Tofacitinib was superior to placebo for the outcomes assessed, and the indirect comparison showed better response in the maintenance phase compared with other biologics. Therefore, a cost-effectiveness analysis would have been the most appropriate. However, the applicant submitted a cost-minimization analysis in which tofacitinib compared with biologics had the lowest cost. In the budget impact analysis, several scenarios were conducted varying comparators, market share and population. In all of them the incorporation of tofacitinib was expected to generate savings in the first year and in five years. Despite the savings expected, the evidence demonstrated that infliximab was superior as induction therapy, and tofacitinib was similar to biologics in the maintenance phase, but there is still no good evidence of safety in the real world. These facts should be considered in decision making.

Initial Recommendation: Conitec, at its plenary session held on April 12th, 2019, decided not to recommend the incorporation of tofacitinib citrate for the treatment of moderate to severe ulcerative colitis in adult patients with inadequate response, loss of response or intolerance to previous treatment with conventional synthetic or biological drugs, in the scope of SUS, due to uncertainty about efficacy and safety.

Public consultation: The Public Consultation No. 83/2019 was held from January 2nd to 21st, 2020. A total of 272 contributions were received, of which 31 were technical-scientific, and 241 were experience or opinion contributions from patients, relatives, friends or caregivers of patients, health professionals or people interested in the subject. The majority disagreed with Conitec's preliminary recommendation, mainly pointing out the clinical efficacy and safety of tofacitinib, the maintenance of remission and endoscopic improvement (healing). They also emphasize that it is an oral synthetic drug, while the comparators are injectable biologics, and it is an option when previous treatment fails. The applicant contributed to the public consultation, and also recalculated the doses and the necessary amount of tofacitinib for the first and following years of treatment, applying these new estimates to both economic evaluation and budget impact. Overall, these contributions were considered important to complement the technical report, especially professionals or patients' experiences with the use of tofacitinib.

Final Recommendation: The Conitec's members present at the 88th Ordinary Meeting, on July 7th, 2020, unanimously decided not to recommend the incorporation of tofacitinib for the treatment of moderate to severe ulcerative colitis in adult patients with inadequate response, loss of response or intolerance to previous treatment with synthetic drugs, in the scope of SUS. After analysing the contributions received in the public consultation, the members of Conitec's plenary session considered the following aspects: although the cost of treatment with tofacitinib could lead to a significant reduction in administration and storage costs, the therapy with infliximab and vedolizumab showed better statistical results in the evaluated outcomes, or they were not considered different from tofacitinib for the outcome of clinical remission at week 8. Moreover, there was no additional scientific evidence that could change the preliminary recommendation, which was mainly based on the uncertainty about efficacy and safety of tofacitinib compared with other options available in SUS. Also, the type of economic evaluation submitted by the applicant proved to be inadequate because the comparator drugs do not have a similar efficacy that would justify the use of cost-minimization analysis. The Deliberation Record No. 530/2020 was signed.

Decision: Not to incorporate tofacitinib citrate for the treatment of moderate to severe ulcerative colitis in adult patients with inadequate response, loss of response or intolerance to previous treatment with synthetic drugs, in the scope of SUS, according to Ordinance No. 22, published in the Official Gazette of the Federal Executive No. 149, Section 1, page 91, on August 5th, 2020.