CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

TOFACINITIB (XELJANZ)
Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a tumor necrosis factor-alpha inhibitor (TNFi).

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that tofacitinib be reimbursed for the treatment of adult patients with moderately to severely active UC with an inadequate response, loss of response, or intolerance to either conventional UC therapy or a TNFi, if the following conditions are met:

Conditions
- The drug plan cost of treatment of UC with tofacitinib 10 mg twice daily not exceed the drug plan costs of treatment of UC with the least costly biologic TNFi.
- Initial treatment of UC with tofacitinib at 10mg twice daily be assessed after 8 weeks of therapy and discontinued if clinical response has not been achieved.
- The prescribing of tofacitinib for the treatment of UC to be restricted to gastroenterologists.

Service Line: CADTH Drug Reimbursement Recommendation
Version: 1.0
Publication Date: March 2019
Report Length: 8 Pages

CADTH

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Tofacitinib (Xeljanz — Pfizer Canada Inc.)

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a tumor necrosis factor-alpha inhibitor (TNFi).

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that tofacitinib be reimbursed for the treatment of adult patients with moderately to severely active UC with an inadequate response, loss of response, or intolerance to either conventional UC therapy or a TNFi, if the following conditions are met:

Conditions

- The drug plan cost of treatment of UC with tofacitinib 10 mg twice daily not exceed the drug plan costs of treatment of UC with the least costly biologic TNFi.
- Initial treatment of UC with tofacitinib at 10 mg twice daily be assessed after 8 weeks of therapy and discontinued if clinical response has not been achieved.
- The prescribing of tofacitinib for the treatment of UC to be restricted to gastroenterologists.

Reasons for the Recommendation

1. In OCTAVE Induction 1 and OCTAVE Induction 2, the proportion of patients with remission at week 8 was greater in the tofacitinib 10 mg arm (18.5% and 16.6%, respectively) compared with placebo (8.2% and 3.6%). The difference in proportion from placebo was statistically significant at 10.3% (95% CI, 4.3% to 16.3%; P = 0.0070) and 13.0% (95% CI, 8.1% to 17.9%; P = 0.0005). In OCTAVE Sustain, the proportion of patients with remission at Week 52 was greater in both the tofacitinib 5 mg and the tofacitinib 10 mg arms (34.3% and 40.6%, respectively) compared with placebo (11.1%). The difference in proportion from placebo was statistically significant at 23.2% (95% CI, 15.3% to 31.2%; P < 0.0001) and 29.5% (95% CI, 21.4% to 37.6%; P < 0.0001).
2. One manufacturer-supplied and two published indirect treatment comparisons suggest no statistically significant differences between tofacitinib and infliximab, adalimumab, golimumab or vedolizumab for the induction of clinical response, remission or mucosal healing in patients with no prior TNFi treatment experience. No conclusions could be drawn with regards to the efficacy of tofacitinib for maintenance therapy, or as induction therapy in patients who were TNFi treatment experienced, due to sparse data or differences in study design and populations enrolled.

Discussion Points

- The committee acknowledged that oral administration of tofacitinib is likely more convenient for some UC patients than the IV infusions and SC injections that are required for some biologic TNFis.
- The committee recognized that requiring the patient to reach remission at 8 weeks of treatment with tofacitinib is not consistent with clinical practice or with the reimbursement criteria that are currently in place for other drugs that are appropriate comparators for tofacitinib.
- The committee discussed the best measure of clinical response at 8 weeks and noted the impracticality of requiring endoscopy at this time point for all patients with UC taking tofacitinib given the limitations associated with timely access and associated costs of health care resources in Canada. While the total Mayo score was used throughout the clinical trials, the requirement for an endoscopy for a total Mayo score makes this measure impracticable to implement as a criterion for reimbursement. In the absence of the Total Mayo score there are two alternatives a) use of the partial Mayo score (which does not require colonoscopy) b) leave the determination for discontinuation to the clinical judgment of prescribing gastroenterologists. The partial Mayo score was not prioritized in the statistical testing hierarchy in the OCTAVE trials and CDEC cannot therefore categorically recommend its use. Therefore, the committee concluded that the determination of whether a patient has achieved a clinical response should be left to the clinical judgement of the prescribing gastroenterologist.
- The clinical experts consulted by CDR noted that clinicians may consider escalating the dosage of tofacitinib to 10 mg twice daily in patients with UC who have an inadequate response to the 5 mg twice-daily dose. This would exceed the recommended

dosage of 5 mg twice daily after the induction phase. The percentage of patients requiring 10 mg twice-daily dosing is unknown but is suggested to increase over time as patients remain on treatment.

- The committee noted the increased risk of infections and infestations in patients in the tofacitinib arms compared with placebo, specifically an increased incidence of infection with Herpes zoster in the 10 mg twice daily tofacitinib arm in OCTAVE Sustain (5.1% compared to 1.0% for the recommended maintenance dose of 5 mg twice daily tofacitinib; and 0.5% for placebo).

Background

Tofacitinib has a Health Canada indication for the treatment of adult patients with moderately to severely active ulcerative colitis with an inadequate response, loss of response or intolerance to either conventional UC therapy or a TNFα inhibitor. Tofacitinib is an immunomodulator that acts as a selective, reversible inhibitor of the Janus kinase (JAK) family. Specifically, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2. It is available as 5 mg and 10 mg tablets (as tofacitinib citrate) and the Health Canada approved dose is 10 mg twice daily for induction for at least 8 weeks and 5 mg twice daily for maintenance therapy. Although, depending on therapeutic response, 10 mg twice daily may also be used for maintenance in some patients, the lowest effective dose possible is recommended for maintenance therapy to minimize adverse events.

Summary of Evidence Considered by CDEC Considerations

The committee considered the following information prepared by the Common Drug Review: a systematic review of RCTs of tofacitinib and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert(s) with experience in treating patients with moderately to severely active ulcerative colitis, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

The Gastrointestinal Society provided input for this submission. Patient perspectives were obtained from questionnaires, online media and conversations with patients during lecture sessions, roundtables, support group meetings, and stories submitted over time. The following is a summary of key input from the perspective of the patient group:

- Ulcerative colitis is associated with considerable physical symptoms and psychosocial impacts; these include diarrhea, cramping abdominal pain, and varying amounts of rectal bleeding, as well as anxiety and stress due to having unpredictable and persistent flares.
- The patient group noted the following issues with current therapies: long-term use of 5-aminosalicylic acid has shown sustained reduction in inflammation among some patients; corticosteroids for topical relief of the colon are available in an inconvenient rectal formulation; suppositories are inefficient if patients have significant diarrhea; immunosuppressive agents may take over six months to show their effects; and biologics require intravenous injections or attending infusion clinics for administration.
- Patients are seeking drugs that are effective in providing sustained remission/treatment response and offer an alternative therapy that could be tried in lieu of proceedingto biologic treatments that are only available via injection or infusion.

Clinical Trials

The systematic review included three phase III randomized placebo control trials of patients with moderately to severely active ulcerative colitis. OCTAVE Induction 1 (N = 614) and OCTAVE Induction 2 (N = 547) randomized patients in a 4:1 ratio for treatment with tofacitinib 10 mg twice daily delivered orally in tablet form or treatment with placebo for eight weeks. In OCTAVE Sustain (N = 593) randomized patients in a 1:1:1 ratio for treatment with tofacitinib 5 mg twice daily delivered orally in tablet form; tofacitinib 10 mg twice daily delivered orally in tablet form; or treatment with placebo for 52 weeks.

Limitations with the reviewed studies included: the statistical analyses of secondary outcome measures across all trials were not adjusted for multiplicity; no active comparator was used across trials (placebo-controlled); withdrawals in the 52-week study were extensive and differential by treatment arm. In the Induction trials, 3% to 13% of patients withdrew from the studies. In OCTAVE Sustain, 43.9%, 35.7% and 73.2% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms discontinued the study. The

greatest proportions of patients that discontinued were within the placebo arms in in OCTAVE Induction 2 and OCTAVE Sustain. Across all trials, study discontinuation was most often attributed to insufficient clinical response.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- Remission; defined as a total Mayo Score of two points or fewer, with no individual subscore exceeding one point and a rectal bleeding subscore of zero.
- Sustained corticosteroid-free remission among patients in remission at baseline; defined as a Mayo Score of two points or fewer, with no individual subscore exceeding one point and a rectal bleeding subscore of zero, in addition to not requiring any treatment with corticosteroids for at least four weeks prior to the visit.
- Clinical remission; defined by a total Mayo Score of two points or fewer, with no individual subscore exceeding one point.
- Clinical response; defined by a decrease from baseline in Mayo Score of at least three points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least one point or absolute subscore for rectal bleeding of zero or one.
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score. The IBDQ assess health related quality of life (HRQoL) in patients with IBD (e.g., UC and Crohn's disease). An absolute score change of ≥ 30 points, or ≥ 15 points above the placebo score was associated with clinical benefits in patients with IBD
- Short Form-36 (SF-36). The SF-36 is a generic self-reported health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health reported quality of life. The SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS). For both PCS and MCS as well as the individual subscale scores in SF-36, an absolute score increases of 3 to 5 points was shown to capture MCIDs in various conditions, including colitis
- Euro Quality of Life 5 Dimensions/Visual Analog Scale (EQ-5D/VAS). The EQ-5D-3L is a generic preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments including IBD. No MCID data was found for patients with ulcerative colitis; however in patients with IBD a MCID of 0.05 for the utility index score and 10.9 for the VAS was determined.
- Harms were assessed as the occurrence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms (e.g., infection with herpes zoster).

The primary outcome in the two Induction trials was remission at Week 8. In OCTAVE Sustain, the primary endpoint was remission at Week 52.

Efficacy

In the Induction trials, tofacitinib was associated with statistically significant differences in the proportion of patients who achieved remission at Week 8 compared with placebo, with absolute differences of 10.3% (95% CI, 4.3% to 16.3%) and 13.0% (95% CI, 8.1% to 17.9) for Induction 1 and 2 respectively. In OCTAVE Sustain at Week 52, the difference in proportion of patients with remission was statistically significant for tofacitinib 5 mg (23.2% 95% CI, 15.3% to 31.2%) and tofacitinib 10 mg (29.5% 95% CI, 21.4% to 37.6%) versus placebo. The trials also showed statistically significant differences between tofacitinib and placebo in the proportion of patients with mucosal healing with absolute differences of 16% to 17% in the Induction trials, and 24% and 33% in the maintenance study. Other outcomes, such as clinical remission and clinical response, which were outside the statistical testing procedures also showed results that favored tofacitinib over placebo, however these data should be interpreted as inconclusive.

In OCTAVE Sustain, a secondary endpoint was sustained corticosteroid-free remission among patients in remission at baseline at Week 52, defined as a Mayo Score of two points or fewer, with no individual subscore exceeding one point and a rectal bleeding subscore of zero, in addition to not requiring any treatment with corticosteroids for at least four weeks prior to the visit. The difference in proportion of sustained corticosteroid-free remission from placebo was statistically significant at 30.3% (95% CI, 17.4% to 43.2%; $P < 0.0001$) and 42.2% (95% CI, 27.9% to 56.5%; $P < 0.0001$) for tofacitinib 5 mg and the tofacitinib 10 mg, respectfully.

The clinical experts consulted for this review determined that the improvement for these outcomes was clinically relevant.

Health related quality of life was identified as an important outcome based on patient input received for this review. Collectively, the results for health related quality of life suggest a difference between tofacitinib and placebo; however limitations in these data prevent conclusions from being made.

Harms (Safety)

Serious adverse events occurred in 3.4% and 4.2% of patients in the tofacitinib 10 mg arm in OCTAVE Induction 1 and OCTAVE Induction 2, respectfully; and in 4.1% and 8.0% of patients in the placebo arm, In OCTAVE Sustain, serious adverse events occurred in 5.1%, 5.6%, and 6.6% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms. The most common serious adverse event related to gastrointestinal disorders; specifically to UC. Adverse events were similar overall between tofacitinib and placebo.

Infections and infestations generally occurred more often in patients in the tofacitinib arms compared with placebo, specifically in the 52-week study OCTAVE Sustain. An increased incidence of infection with Herpes zoster was observed in the 10 mg tofacitinib arm in OCTAVE Sustain (5.1% compared to 1.0% for the recommended maintenance dose of 5 mg tofacitinib; and 0.5% for placebo). Infection with Herpes zoster in the OCTAVE Induction 1 and OCTAVE Induction 2 occurred in 0.6% and 0% of patients in the tofacitinib 10 mg arms, respectively; compared with 0.8% and 1.0% in the placebo arms.

Withdrawals due to adverse events occurred in 3.8% and 4.0% of patients in the tofacitinib 10 mg arm in OCTAVE Induction 1 and OCTAVE Induction 2, respectfully; and in 1.6% and 7.1% of patients in the placebo arm, In OCTAVE Sustain, withdrawals due to adverse events occurred in 9.1%, 9.7%, and 18.7% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms. The most common serious adverse event related to gastrointestinal disorders; specifically to worsening of UC.

Indirect Treatment Comparisons (ITC)

One manufacturer-supplied ITC and two published ITCs were identified. All reports compared tofacitinib to biologic agents approved for use in Canada for the treatment of moderate to severe UC.

The manufacturer submitted ITC used Bayesian methods to conduct the ITC. A number of issues were identified regarding the ITC analyses, particularly for the analysis of maintenance therapy, which relied on imputed data in order to pool data from studies that used an enrichment design to those using a standard parallel design. Except for the analysis of induction therapy in the TNFi naïve population, the networks were sparse, often with only one study (or subgroup data from one study) per comparison. Moreover, the use of probit scores, made it difficult to interpret the clinical relevance of the results.

Bonovas et al. (2018) and Singh et al. (2018) used non-Bayesian methods to conduct the ITCs, and reported similar results, with minor differences likely due to inclusion of different studies for some analyses. With the exception of the analysis of induction therapy in TNFi naïve patients, the results of the NMA showed high uncertainty, due to the sparse network and low frequency of some events.

Based on the three ITCs, no conclusions can be drawn with regards to the relative treatment effects of maintenance therapy, due to differences in study design, populations enrolled, and sparse data.

No statistically significant differences were detected in the relative risk of adverse events, serious adverse events or infection based on indirect evidence for tofacitinib versus biologic agents, although the data suggests a possible increased frequency of infection for tofacitinib versus placebo.

Based on indirect evidence, no statistically significant differences were found between tofacitinib and infliximab, adalimumab, golimumab or vedolizumab for the induction of clinical response, remission or mucosal healing in patients with no prior TNFi treatment experience. The relative efficacy of induction therapy for patients who were TNFi treatment experienced showed high uncertainty due to the sparse data. Thus conclusions on these data cannot be made.

Cost and Cost-Effectiveness

Tofacitinib is administered as one 10 mg tablet twice daily during an induction period lasting at least 8 weeks, followed by one 5 mg tablet administered twice daily thereafter during the maintenance phase of treatment once response to treatment has been achieved. At the manufacturer submitted price of $23.96 per 5 mg tablet and $42.34 per 10 mg tablet, the annual cost of tofacitinib is $19,501 in the first year and $17,442 every year thereafter based on recommended dosing for induction and 5 mg twice daily in the maintenance phase. This cost could increase significantly, up to $30,181 per year, in certain populations requiring tofacitinib 10 mg twice daily in the maintenance phase.

The manufacturer submitted a cost-utility analysis comparing tofacitinib plus conventional therapy (a mix of 5-aminosalicylates, corticosteroids, and immuno-modulators) to biologic treatments (TNFi's: vedolizumab, infliximab, infliximab biosimilar, adalimumab, and golimumab) plus conventional therapy, as well as conventional therapy alone in adults with moderately to severely active UC with an inadequate response to conventional therapy or biological agent. The analysis was conducted over a lifetime time horizon from the Canadian public health care payer perspective. In the manufacturer's Markov state-transition cohort model, patients with active UC started an 8-week induction period with tofacitinib or a biologic comparator with conventional therapy or continued on conventional therapy alone. At any time in the model, patients could experience a response (≥3 point decrease from baseline Mayo score and ≥30%, and ≥1 point decrease in rectal bleeding sub-score or absolute rectal bleeding sub-score of zero or one) or clinical remission (total Mayo score of ≤2 points, with no individual sub-score exceeding 1 point), remain in an active UC state (non-responders), and responders could lose their response and regress to active UC. Patients with active UC could undergo a colectomy at any time. The two populations of interest (biologic-exposed and biologic-naïve) were modelled separately, and combined into a weighted mixed population analysis (53.9% biologic-exposed and 46.1% biologic-naïve patients as observed in the manufacturer's induction trials). Biologic-naïve patients who did not respond to tofacitinib or biologic treatment after an 8-week induction period were switched to a different biologic agent (vedolizumab in all cases, or infliximab for patients starting on vedolizumab). If they did not respond to a second agent, they received conventional therapy alone. Biologic-exposed patients who did not respond to tofacitinib or biologic agent received conventional therapy. An ITC submitted by the manufacturer was used to inform the treatment efficacy of tofacitinib and all included comparators. The manufacturer reported that when compared to adalimumab, infliximab biosimilar, and continuing conventional UC therapy for a mixed population of biologic-exposed and -naïve patients, tofacitinib is associated with incremental cost-utility ratios of $8,897, $145,184, and $118,387 per QALY gained, respectively. The manufacturer reported tofacitinib had fewer costs and more QALYs (i.e., dominant) when compared with vedolizumab, infliximab, and golimumab in the mixed population.

CADTH identified the following key limitations with the manufacturer's submitted economic analysis:

- The comparative treatment effect of tofacitinib with relevant comparators, particularly in the maintenance phase, are uncertain given the limitations the CADTH clinical reviewers identified with the tofacitinib studies and the manufacturer-submitted ITC
- Modeling of treatment sequences in biologic-naïve patients bias in favor of tofacitinib by including a different second-line of treatments for tofacitinib compared with comparator treatments
- The post-colectomy health state utility value was lower than the utility value for patients with active ulcerative colitis which does not appear to be appropriate (does not meet face validity)
- Adverse event risks were applied in the 8-week induction phase only despite evidence of adverse events occurring in the maintenance studies.

CADTH conducted separate re-analyses for biologic-naïve and -exposed patients. For biologic-naïve patients, conventional therapy is the optimal therapy where the decision maker is willing to pay less than $166,608 per QALY and infliximab biosimilar is the optimal therapy where the decision maker is willing to pay more than $166,608 per QALY. Tofacitinib was dominated by infliximab biosimilar (i.e., tofacitinib is more costly and associated with less QALYs than infliximab biosimilar). For biologic-exposed patients, conventional therapy is the optimal therapy where the decision maker is willing to pay less than $143,710 per QALY and tofacitinib is the optimal therapy where the decision maker is willing to pay more than $143,710 per QALY. Price reductions of 44% and 74% would be required for tofacitinib to be the optimal treatment at a willingness-to-pay of $50,000 per QALY in the biologic-exposed and biologic naïve populations, respectively. CADTH reanalyses could not address several important limitations, including those related to treatment efficacy and duration of treatment effect, and as such, the results of this economic evaluation should be viewed with caution.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 21, 2018 Meeting

Regrets

None

Conflicts of Interest

None

February 20, 2019 Meeting

Regrets

None

Conflicts of Interest

None