CDEC FINAL RECOMMENDATION

TOFACITINIB
(Xeljanz — Pfizer Canada Inc.)
Indication: Rheumatoid Arthritis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that tofacitinib be listed, in combination with methotrexate (MTX), for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA or as monotherapy in those who were intolerant to MTX, if the following clinical criterion and conditions are met:

Clinical criterion:
- Inadequate response or intolerance to non-biologic disease-modifying antirheumatic drugs (DMARDs).

Conditions:
- List in a similar manner to biologic DMARDs
- Daily dosage not to exceed 10 mg (i.e., 5 mg twice daily)
- Drug plan cost for tofacitinib not to exceed the drug plan costs for the biologic DMARDs reimbursed.

Reasons for the Recommendation:
1. Five double-blind randomized controlled trials (RCTs) conducted in patients with active RA demonstrated that treatment with tofacitinib, with or without background DMARD therapy, was superior to placebo for achieving clinical response as measured using the American College of Rheumatology (ACR) 20, ACR 50, and ACR 70 criteria.
2. Similar to biologic DMARDs used to treat RA, tofacitinib is associated with an increased risk of harm, including malignancies and serious infections.
3. At the submitted price of $23.10 per 5 mg tablet ($46.19 per day), the CADTH Common Drug Review (CDR) estimates that treatment with tofacitinib is more costly than treatment with subsequent entry biologic infliximab (Inflectra), intravenous (IV) tocilizumab, and subcutaneous (SC) tocilizumab, with incremental costs ranging from $1,272 to $8,718 in the first year of treatment for patients weighing 70 kg.

Background:
Tofacitinib is a Janus kinase inhibitor approved by Health Canada for reducing the signs and symptoms of RA, in adult patients with moderately to severely active RA who have had an inadequate response to MTX. It is approved for use as a 5 mg oral tablet taken twice daily, either alone (if the patient has had an intolerance to MTX) or in combination with MTX.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of tofacitinib, a critique of the manufacturer's pharmacoeconomic evaluation, and information submitted by patient groups about outcomes and issues important to individuals living with RA.

Patient Input Information
The following is a summary of information provided by three patient groups that responded to the CDR call for patient input:

- RA is an inflammatory condition involving swelling, pain, and joint destruction, which may require major surgery on affected joints. Pain is often the most concerning symptom, causing difficulty with activities of daily living, relationships, employment, and leisure activities.
- Current treatments for RA include DMARDs (biologic and non-biologic), nonsteroidal anti-inflammatory drugs, corticosteroids, and analgesics. These treatments have important adverse effects, including fever, night sweats, nausea, vomiting, fatigue, easy bruising or bleeding, dizziness, itching, weight loss, stomach pain, pale skin, shortness of breath, rapid heart rate, loss of appetite, jaundice, dry skin, hair loss, and suppression of the immune system.
- Patients often require multiple drugs in combination to manage their RA. When patients respond to treatment, it can be very effective, yet for others, current therapies are partially or completely ineffective. Benefits also frequently wane over time. Patient groups emphasized that having a range of treatment options increases the likelihood that patients will have access to affordable and effective medication with fewer side effects.
- For some patients, oral administration is more convenient than the IV or SC administration that is required for biologic DMARDs, and also allows patients to avoid some adverse effects, such as injection-site reactions, vein scarring, and scar tissue.

Clinical Trials
The CDR systematic review included five manufacturer-sponsored, double-blind RCTs evaluating the efficacy and harms of tofacitinib 5 mg twice daily, 10 mg twice daily, and adalimumab (only in Study 1064) versus placebo. One study was performed in patients who had previously experienced an inadequate response to one or more tumour necrosis factor (TNF) inhibitors (Study 1032), and the others were performed in patients who had experienced an inadequate response to non-biologic DMARDs and/or MTX (studies 1044, 1045, 1046, and 1064). Tofacitinib was administered as monotherapy in Study 1045 and given with background DMARDs in the studies 1032, 1044, 1046, and 1064. The double-blind periods of the studies were six to 24 months in duration; however, early escape was permitted in the placebo groups at three months. In accordance with the dosage regimen recommended in the Health Canada–approved product monograph, the tofacitinib data presented in this report are limited to the 5 mg twice-daily treatment groups.

Outcomes

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

- ACR 20 response rate — defined as the proportion of patients who demonstrated a ≥ 20% improvement in tender and swollen joint counts and ≥ 20% improvement from baseline in three of the five remaining ACR core set measures: patient global assessment of arthritis, physician global assessment of arthritis, patient assessment of arthritis pain, Health Assessment Questionnaire–Disability Index (HAQ-DI), and C-reactive protein (CRP).
- ACR 50 and ACR 70 response rates — similar to the ACR 20, but with improvements of ≥ 50% and ≥ 70%.
- HAQ-DI — assesses the degree of difficulty a patient had experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. The minimal clinically importance difference (MCID) is estimated to be 0.22.
- Disease Activity Score (DAS) Assessments — evaluates disease activity using the following measures: tender/painful joint count (28 joints); swollen joint count (28 joints); CRP or erythrocyte sedimentation rate (ESR); and patient global assessment of arthritis (for DAS28-4 [ESR]). Response rates were calculated for the proportion of patients achieving a DAS28-4(ESR)<2.6 or a DAS28-4(CRP)<2.6.
- Modified Total Sharp Scores (mTSS) — measures the presence of erosions in the hands and feet and the presence of joint space narrowing in the hands, wrists, and feet. The scores for each feature for the individual joints are summed. For erosion scores, 16 locations in each hand and wrist and 12 locations in each foot were scored using a six-point scale from 0 to 5. For joint space narrowing, 15 locations in each hand and wrist and six locations in each foot were scored using a five-point scale from 0 to 4.
- Short-Form 36 (SF-36) — a 36-item generic health status instrument that measures eight general health domains: physical functioning, role physical (PCS), bodily pain, general health, vitality, social functioning, role emotional, and mental health (MCS). Higher scores indicate better health-related quality of life. The eight sub-domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. The MCID is estimated to be 2.5 to 5 points.
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale — a patient-completed questionnaire, consisting of 13 items, that evaluates fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (i.e., less fatigue). A suggested MCID for the FACIT-Fatigue scale in RA patients is between 3 and 4 points.

All five trials used the same three measures for the co-primary end points (ACR 20, HAQ-DI, and the rate achieving DAS28-4[ESR]<2.6). The co-primary end point of ACR 20 response was evaluated at three months (studies 1032 and 1045) or six months (studies 1044, 1046, and 1064). The co-primary end point of change from baseline for HAQ-DI was evaluated at three months in all trials. The co-primary end point of DAS28-4(ESR)<2.6 was evaluated at three months (studies 1032 and 1045) or six months (studies 1044, 1046, and 1064). Study 1044 used a fourth co-primary end point of mTSS. No other studies measured radiographic outcomes.

Efficacy

Inadequate Response to Tumour Necrosis Factor Inhibitor (Study 1032)

- A statistically significantly greater proportion of tofacitinib-treated patients demonstrated ACR 20, ACR 50, and ACR 70 responses compared with placebo-treated patients: ACR 20 (42% versus 25%; *P* = 0.0025), ACR 50 (27% versus 8%; *P* < 0.0001), and ACR 70 (13% versus 2%; *P* < 0.0001).
- Tofacitinib was statistically superior to placebo for improvements in HAQ-DI (mean difference [MD] −0.3; 95% confidence interval [CI], −0.4 to −0.1), DAS28-4(ESR)<2.6 (7% versus 2%); DAS28-4(CRP)<2.6 (20% versus 5%), SF-36–MCS (MD 3.15; 95% CI, 0.87 to 5.43), SF-36–PCS (MD 3.63; 95% CI, 1.94 to 5.31), and FACIT-Fatigue Scale (MD 5.15; 95% CI, 2.77 to 7.54).

Inadequate Response to DMARD/MTX

Tofacitinib as Monotherapy (Study 1045)

- A statistically significantly greater proportion of tofacitinib-treated patients achieved ACR 20, ACR 50, and ACR 70 responses compared with placebo-treated patients: ACR 20 (60% versus 27%; *P* < 0.0001); ACR 50 (31% versus 13%; *P* < 0.0001); and ACR 70 (15% versus 6%; *P* = 0.0026).
- Tofacitinib was statistically superior to placebo for improvements in HAQ-DI (MD −0.3; 95% CI, −0.4 to −0.2), DAS28-4(CRP)<2.6 (19% versus 5%), SF-36–MCS (MD 3.02; 95% CI, 0.93 to 5.12), SF-36–PCS (MD 4.16; 95% CI, 2.33 to 5.99), and FACIT-Fatigue (MD 3.86; 95% CI, 1.93 to 5.78). There was no statistically significant difference in achieving DAS28-4(ESR)<2.6 (*P* = 0.618).

Tofacitinib in Combination with DMARDs (Studies 1044, 1046, and 1064)

- The proportion of patients achieving ACR 20, ACR 50, and ACR 70 responses was larger in the tofacitinib groups compared with placebo at six months (all *P* < 0.0001):
  - Study 1044: ACR 20 (52% versus 26%), ACR 50 (32% versus 8%), and ACR 70 (15% versus 1%)
  - Study 1046: ACR 20 (53% versus 31%), ACR 50 (34% versus 13%), and ACR 70 (13% versus 3%)
  - Study 1064: ACR 20 (52% versus 28%), ACR 50 (37% versus 12%), and ACR 70 (20% versus 2%).
- In Study 1064, adalimumab also demonstrated statistical superiority versus placebo for ACR 20, ACR 50, and ACR 70 responses. The proportion of ACR 20 responders was similar in the adalimumab and tofacitinib groups at six months and 12 months.
- Across all three studies, tofacitinib was generally statistically superior to placebo for improvements in HAQ-DI, DAS28-4(ESR)<2.6, DAS28-4(CRP)<2.6, SF-36–MCS, SF-36–PCS, and FACIT-Fatigue, with the exception of the HAQ-DI and DAS28-4(ESR)<2.6 in study 1044, in which statistical significance was not evaluated due to the hierarchal testing procedure.
- Both the tofacitinib and placebo groups demonstrated increased (i.e., worsening) mTSS scores from baseline and there was no statistically significant difference between the two groups at six months (MD −0.34; 95% CI, −0.73 to 0.04) or 12 months (MD −0.63; 95% CI, −1.27 to 0.02).

Harms (Safety and Tolerability)

- In the first three months of the included trials, the proportion of patients who experienced at least one adverse event ranged from 49% to 53% in the tofacitinib groups, 47% to 61% in the placebo groups, and 52% in the adalimumab group.
- Serious adverse events ranged from < 1% to 6% in the tofacitinib groups, 2% to 5% in the placebo groups, and 3% in the adalimumab group.
- Withdrawals due to adverse events ranged from 1% to 7% in the tofacitinib groups, 1% to 5% in the placebo groups, and 5% in the adalimumab group.
- In the first three months of the included trials, serious infections were reported in one patient (0.6 events per 100 patient-years) who received placebo and in eight patients (2.8 events per 100 patient-years) who received 5 mg twice daily of tofacitinib. The overall frequency of infections was 20% in the 5 mg twice-daily tofacitinib group, and 18% in the placebo group. The most commonly reported infections were upper respiratory tract infections and nasopharyngitis, and urinary tract infections.
- Malignancies (excluding non-melanoma skin cancer) were reported for two (0.2%) patients (0.7 events per 100 patient-years) who received tofacitinib and no patients who received placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing the drug cost of tofacitinib 5 mg twice daily to biologic DMARDs: adalimumab, etanercept, golimumab, infliximab, abatacept, certolizumab pegol, tocilizumab, anakinra, and rituximab in patients with moderately to severely active RA who have had an inadequate response to MTX. The assumption of similar efficacy and safety among agents was based on Study 1064 and a manufacturer-funded mixed treatment comparison with other biologic DMARDs. The analysis was conducted from the Canadian public payer perspective over a two-year time horizon. Only drug acquisition costs were considered and these were obtained from the Ontario Exceptional Access Program. Administration costs for injectable drugs were not included. The manufacturer submitted a price of $23.0965 per 5 mg tablet ($46.19 daily).

CDR identified the following key limitations with the manufacturer's economic submission:

- The comparative efficacy and safety of tofacitinib compared with biologic DMARDs beyond 12 weeks are uncertain.
- Overestimation of the cost of IV tocilizumab by the manufacturer led to an underestimation of the total incremental costs of tofacitinib when compared with tocilizumab.
- For the biologic DMARDs that are dosed based on weight, the manufacturer considered only a weight of 70 kg or 100 kg, except for abatacept. CDR considered a broader range of weights (50 kg, 70 kg, and 101 kg) to better assess the differential cost of tofacitinib compared with biologic DMARDs.

At the current daily cost of $46.19 ($16,872 annually), and using an average patient weight of 70 kg, based on CDR reanalyses, tofacitinib is expected to result in cost savings ranging from $495 to $6,829 in the first year of treatment when compared with adalimumab, certolizumab pegol, etanercept, golimumab, infliximab (Remicade), anakinra, abatacept, and two courses of rituximab. When compared with subsequent entry biologic infliximab (Inflectra), tocilizumab IV 4 mg/kg every four weeks, and tocilizumab SC every other week, tofacitinib is expected to result in incremental costs ranging from $1,272 to $8,718 in the first year of treatment. The ability of

tofacitinib to result in cost savings is affected by patient weight and escalated dosing regimens: in a 50 kg patient, tofacitinib is more expensive than most weight-based biologics except infliximab when used at a dose up to 10 mg/kg and tocilizumab SC using a weekly dosing regimen. However, using a patient weight of 101 kg, tofacitinib is less expensive than most biologics except tocilizumab IV at a dose of 4 mg/kg every four weeks.

Other Discussion Points:

CDEC noted the following:

- Tofacitinib is administered orally, which is more convenient for some patients than the IV infusions and SC injections that are required for some biologic DMARDs.
- The clinical expert consulted by CDR noted that clinicians may consider escalating the dosage of tofacitinib to 10 mg twice daily in patients who have an inadequate response to the 5 mg twice-daily dose. This would exceed the recommend dosage of 5 mg twice daily.
- The early escape criteria used in the clinical trials limit the ability to make comparisons beyond three months of treatment.
- The European Medicines Agency refused to grant market authorization for tofacitinib, concluding that the benefits did not outweigh the harms.
- Treatment with tofacitinib is associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein cholesterol. The product monograph states that the effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined and that assessment of lipid parameters should be performed at baseline, four to eight weeks following initiation, and every six months thereafter.
- Inhibiting the progression of structural damage is an important treatment objective for RA; however, no statistically significant improvements in radiographic scores were observed in Study 1044 for tofacitinib versus placebo.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no studies designed to evaluate the safety and efficacy of tofacitinib compared with biologic DMARDs.
- The long-term safety profile of tofacitinib requires further evaluation.
- The safety and efficacy of tofacitinib have not been evaluated in patients older than 70 years.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 18, 2015 Meeting

Regrets:

One CDEC member was unable to attend the meeting.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

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