CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BARICITINIB (OLUMIANT — ELI LILLY CANADA INC.)
Indication: For use in combination with methotrexate (MTX) for the treatment of adult patients with moderate to severe rheumatoid arthritis (RA) who have responded inadequately to one or more disease-modifying anti-rheumatic drugs (DMARDs). Baricitinib may also be used as monotherapy in cases of intolerance to MTX.

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that baricitinib be reimbursed for use in combination with MTX for the treatment of adult patients with moderate to severe RA who have responded inadequately to one or more DMARDs, if the following conditions are met:

Conditions for Reimbursement

Initiation Criteria

1. Adult patients with moderately to severely active RA on stable doses of DMARDs who have had inadequate response or intolerance to one or more DMARDs.
2. Baricitinib should only be used in combination with MTX (alone or with other conventional DMARDs [cDMARDs]).
3. Baricitinib should not be used in combination with other biologic DMARDs (bDMARDs), including Janus kinase (JAK) inhibitors.

Discontinuation Criteria

1. Discontinue treatment if no response by 12 weeks. A response to treatment is defined as an achievement of an American College of Rheumatology (ACR) improvement criteria of at least 20% [ACR20] by week 12.

Prescribing Conditions

1. Patient should be under the care of a rheumatologist.
2. Daily dosage of baricitinib not to exceed 2 mg.

Pricing Conditions

1. The drug plan cost of treatment with baricitinib should result in cost-savings compared with the drug plan cost of treatment with the least costly alternative bDMARD.

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Reasons for the Recommendation

1. In two double-blind, randomized controlled trials (BEACON and BUILD), the percentage of patients achieving ACR20 at week 12 was statistically significantly higher in those allocated to baricitinib compared with placebo: BEACON (48.9% versus 27.3%; odds ratio, 2.7 [95% confidence interval (CI), 1.7 to 4.2], $P = 0.001$); BUILD (65.9% versus 39.5%; odds ratio, 3.0 [95% CI, 2.0 to 4.4], $P = 0.001$). Subgroup analyses performed in BEACON showed a statistically significant benefit versus placebo in patients with lack of efficacy to prior bDMARDs (ACR20 at 12 weeks was 49.1% versus 27.1%) and for patients with previous adverse events (AEs) with bDMARDs (ACR20 at 12 weeks was 45.5 versus 25.0%).
2. The results of both the manufacturer's cost-effectiveness analysis and the CADTH Common Drug Review's (CDR's) base-case analysis showed that for both cohorts of patients with moderate to severe RA, at the submitted price baricitinib is not cost-effective compared with other alternatives. Given the absence of head-to-head trials demonstrating additional clinical benefit of baricitinib over other currently reimbursed alternatives, there is no rationale for baricitinib to be more costly than the least costly treatment alternative.
3. CDEC did not identify that baricitinib addressed an unmet need not already met by another JAK inhibitor or bDMARD product currently reimbursed for the treatment of RA.

Discussion Points

1. CDEC noted that, including baricitinib, there are now ten bDMARDs approved for the treatment of moderate-to-severe RA in Canada. Baricitinib is the second JAK inhibitor in Canada. The other is tofacitinib. There is no direct evidence to suggest that baricitinib offers clinical benefit over tofacitinib or other existing bDMARDs. The network meta-analyses (NMAs) evaluated by CDR found no significant difference between baricitinib, tofacitinib, and other bDMARDs in terms of achieving ACR responses.

2. Results from a manufacturer-submitted NMA [redacted]. Two additional published NMAs were reviewed and had results generally consistent with that of the manufacturer's submitted analysis.
3. CDEC noted limitations associated with the manufacturer-submitted NMA: heterogeneity of study designs and populations and omission of any harms analysis. Therefore, interpretation of the NMA findings on the comparative efficacy of baricitinib with other DMARDs should be considered with caution.
4. CDEC noted that in both the BEACON and BUILD trials, there was no subgroup analysis performed for patients with prior MTX intolerance. This was considered a clinically important evidence gap by CDEC given that baricitinib is indicated for use as monotherapy.
5. CDEC noted that the risk of harms did not appear to differ between baricitinib and placebo with the exception of low neutrophil counts, as seen with 6% of baricitinib patients and 2% of placebo patients in BEACON and 8% of baricitinib patients versus 4% of placebo patients in BUILD.

Background

Baricitinib has a Health Canada indication, in combination with MTX, for treatment of adult patients with moderate to severe RA who have responded inadequately to one or more DMARDs. Baricitinib may also be used as monotherapy in cases of intolerance to MTX. Baricitinib is a JAK inhibitor. It is available as orally administered tablets and the Health Canada–approved dosage is 2 mg once daily.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CDR: a systematic review of double-blind randomized controlled trials of baricitinib and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with RA, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Three patient groups, The Arthritis Society of Canada, Canadian Arthritis Patient Alliance, and Arthritis Consumer Experts, provided input for this submission. Patient perspectives were obtained from a social media request for information, interviews, and a survey. The following is a summary of key input from the perspective of the patient group(s):

- Several patients reported that despite the wide range of currently available medications, most have limited benefits regarding pain and fatigue — the symptoms with the greatest adverse effects on quality of life. Improvement in these outcomes would enhance their ability to work and carry on activities of daily living as well as their social roles within the family.
- Patients reported having to try multiple medications before finding one that works, and once they do find one that works they may eventually experience loss of efficacy. Aside from lack of efficacy, major drawbacks of existing therapies include side effects and cost. The side effects singled out include gastrointestinal symptoms, increased infection risk, and injection site reactions. Cost is also a concern as patients often incur the direct costs of therapy as well as numerous indirect costs such as loss of income from taking time off and travel to appointments, including both those for specialist follow-up and to receive infusions and lab work up.
- The most common sentiment regarding baricitinib was that it represented another option for RA if others were exhausted. Patients also see potential for enhanced efficacy with baricitinib, specifically with respect to managing pain and anti-inflammatory effects and improving fatigue. Ease of administration was also seen as a potential improvement with baricitinib compared with infusions and injections, which were seen as painful and time consuming. Four patients had experience with baricitinib and reported positive experiences and that it represented a "real improvement" over existing therapies.

Clinical Trials

The systematic review included two double-blind randomized placebo-controlled trials of patients with RA. BEACON (N = 527, three groups) and BUILD (N = 684, three groups) both enrolled patients with adult-onset RA who had insufficient response or were intolerant to cDMARDs (BUILD), or who had a stable dosage on background cDMARDs but had insufficient response or intolerance to at least one bDMARD TNF inhibitor (BEACON). Both studies were conducted between 2013 and 2014, in Europe, Asia, and the Americas (including sites in Canada), and had identical trial design: a 24-week, parallel, double-blind treatment period in which baricitinib 2 mg and baricitinib 4 mg were compared with placebo. The Health Canada–approved baricitinib 2 mg dose was the focus of this review.

Major limitations included a lack of active comparators in the included studies, and a relatively short duration of follow-up (24 weeks) for a drug with a relatively novel mechanism of action, but insufficient evidence on long-term effectiveness and safety, particularly with safety issues such as thrombosis and Herpes Zoster noted at the higher 4 mg dose. There was a relatively higher proportion of premature withdrawals in the placebo group than in the baricitinib group (18% versus 10%, respectively) in BEACON. Withdrawals were 13% with placebo and 9% with baricitinib in BUILD. There was a large proportion of patients who opted for rescue therapy with baricitinib 4 mg after 16 weeks, particularly in the placebo groups in both BEACON (22% versus 32% of patients) and BUILD (9% versus 24%), baricitinib versus placebo, respectively. There was no subgroup analysis performed for patients with prior MTX intolerance, a potential gap given that baricitinib may be used as monotherapy in these patients.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: ACR responses (ACR20), the Health Assessment Questionnaire-Disability Index, Disease Activity Scale and high sensitivity C-reactive protein (DAS28-hsCRP), and the Simplified Disease Activity Index (SDAI). The primary outcome in both trials was the percentage of patients achieving an ACR20 response at week 12.

- The primary outcome in each study was the proportion of patients achieving an ACR20 response at 12 weeks, while key secondary outcomes, all assessed at 12 weeks, included the Health Assessment Questionnaire-Disability Index (HAQ-DI), the DAS28-hs-CRP, and the SDAI.
- The ACR criteria provide a composite measure of improvement in both swollen and tender joint counts and at least three of five additional disease criteria: patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, health assessment questionnaire (HAQ), and levels of either C-reactive protein (CRP) or erythrocyte sedimentation rate. ACR20, 50, or 70 responses represent at least a 20%, 50%, or 70% improvement, respectively.
- The change from baseline to week 12 in HAQ-DI scores was a secondary outcome of both included studies. The full HAQ collects data on five generic patient-centered health dimensions: to avoid disability, to be free of pain and discomfort, to avoid adverse treatment effects, to keep dollar costs of treatment low, and to postpone death, while the HAQ-DI is the disability assessment component of the HAQ. There are 20 questions in eight categories to assess a patient's physical functional status: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. For each of these categories, patients report the amount of difficulty they have in performing specific activities, and their responses are made on a scale from zero (no difficulty) to three (unable to do). The most commonly cited meaningful clinically important difference is 0.22; however, lower values have been reported.
- The DAS28 is based on a 28-joint count that includes hands, wrists, elbows, shoulders, and knees. It omits the feet and ankle joints. In recent years, CRP has been used to calculate the DAS28 in place of erythrocyte sedimentation rate. A DAS28 score of 5.1 or greater is considered high disease activity, while a DAS28 score lower than 3.2 indicates low disease activity state and a DAS28 score lower than 2.6 indicates remission.
- The SDAI is a tool for measuring disease activity that integrates measures of physical examination, acute phase response, patient self-assessment, and evaluator assessment; the percentage of patients achieving remission (score of 3.3 or less) on the SDAI was assessed. The SDAI is calculated by adding scores from the following assessments: number of tender joints (0 to 28); number of swollen joints (0 to 28); CRP in mg/dL (0.1 to 10.0); Patient Global Assessment of Disease Activity Visual Analog Scale (0 to 10.0 cm); Physician Global Assessment of Disease Activity Visual Analog Scale (0 cm to 10.0 cm).

Efficacy

In both BEACON (48.9% of baricitinib and 27.3% of placebo) and BUILD (65.9% versus 39.5%) there were more participants in the baricitinib group than in the placebo group that achieved ACR20 and these differences were statistically significant between groups in both BEACON (odds ratio, 2.7 [95% CI, 1.7 to 4.2], *P* = 0.001) and BUILD (odds ratio, 3.0 [95% CI, 2.0 to 4.4], *P* = 0.001). Although other ACR outcomes were exploratory and not controlled for multiplicity, a higher proportion of baricitinib patients versus placebo patients achieved ACR50 at 12 weeks in BEACON (20.1% versus 8.0%) and BUILD (33.6% versus 12.7%) and also at 24 weeks in BEACON (23.0% versus 13.1%) and BUILD (41.5% versus 21.5%). ACR70 responses were achieved by a higher proportion of baricitinib versus placebo patients in BEACON (12.6% versus 2.3%) and in BUILD (17.9% versus 3.1%) at 12 weeks and at 24 weeks (BEACON, 13.2% versus 3.4%; BUILD, 25.3% versus 7.9%). Subgroup analyses of interest to this review were performed on the primary outcome (ACR20 responses at week 12) based on prior reason for failure on bDMARDs (lack of efficacy, AE, other) and for number of previous bDMARDS in BEACON. Results for the lack of efficacy subgroup, baricitinib versus placebo, were 49.1% versus 27.1%, respectively.

In each of the studies baricitinib reduced (improved) scores on the HAQ-DI from baseline to week 12 when compared with placebo, and these differences were statistically significant in both BEACON (least square mean difference between groups of –0.20 [95% CI, –0.32 to –0.08], *P* = 0.001) and in BUILD (least square mean difference between groups of –0.21 [95% CI, –0.30 to –0.11], *P* = 0.001).

Generic health-related quality of life instruments were assessed as exploratory outcomes: Short Form 36 (SF-36) survey and EuroQol 5-Dimensions questionnaire (EQ-5D). There were no statistically significant differences between baricitinib and placebo groups for the SF-36 mental component summary at week 12 or 24. Physical component scores increased (improved) from baseline in each of the groups in BEACON and BUILD. The least square mean difference between baricitinib and placebo at 24 weeks in BEACON was 4.3 (95% CI, 2.6 to 6.1) and in BUILD was 3.7 (95% CI, 2.0 to 5.4). On the EQ-5D Health State Index/Self Perceived Health score, both the baricitinib and placebo groups experienced an increase (improvement) in score from baseline; in BEACON, the least square mean difference between groups was 0.049 (95% CI, 0.018 to 0.081) and in BUILD it was 0.013 (95% CI, 0.023 to 0.075). Similar results were reported when the UK algorithm was used.

In each study, baricitinib reduced (improved) DAS28-hsCRP scores versus placebo and these differences between groups were statistically significant in BEACON (least square mean difference between groups of –0.66 [95% CI, –0.96 to –0.35] *P* = 0.001) and in BUILD (least square mean difference between groups of –0.75 [95% CI, –0.97 to –0.53] *P* = 0.001).

In BUILD, the proportion of patients achieving a clinically significant improvement in SDAI was higher with baricitinib than with placebo (9.2% versus 0.9% of patients) and this difference was statistically significant (odds ratio not reported, *P* = 0.001). In BEACON, there was no statistically significant difference between groups.

Harms (Safety)

In both included trials, there were similar serious AEs with baricitinib compared with placebo. Overall AEs occurred in 71% of baricitinib patients and 64% of placebo patients in BEACON, while in BUILD the percentages were 67% in baricitinib and 71% in the placebo groups. The most common AE was upper respiratory tract infection. Notable harms included infections, which occurred in 44% of baricitinib patients and 31% of placebo patients in BEACON and 31% of baricitinib versus 35% of placebo patients in BUILD. Serious infections occurred in 3% of patients in each group in BEACON and 3% of baricitinib and 2% of placebo patients in BUILD. Other notable harms included malignancies, thrombotic events, dyslipidemia, and elevations in hepatic enzymes, and there were very few events and no clear differences between groups within BEACON and BUILD. There was a numerical higher risk of elevated platelet counts with baricitinib treatment versus placebo in BUILD (19% versus 5%); however, there was a much smaller difference between groups in BEACON (18% versus 14%). Low neutrophil counts were seen with 6% of baricitinib patients and 2% of placebo patients in BEACON and 8% of baricitinib versus 4% of placebo in BUILD.

Indirect Treatment Comparisons

CDR reviewed numerous NMAs involving baricitinib. The manufacturer submitted an NMA that found [redacted]. The two additional published NMAs that were reviewed had results consistent with that of the manufacturer's submitted analysis.

Cost and Cost-Effectiveness

Baricitinib is available as a 2 mg tablet with a recommended dose of 2 mg daily. At the submitted price of $47.92 per 2 mg tablet, the annual cost of baricitinib is $17,490.

The manufacturer submitted a cost-utility analysis for baricitinib for patients with RA based on a discrete-event simulation model in which the time until the first event (death or treatment failure and transition to new treatment) was calculated for each patient. Clinical response to each line of treatment was based on the proportion of patients achieving different ACR response categories (ACR20, ACR50, and ACR70), while HAQ scores and discontinuation were also key considerations within the submitted model. The analysis was conducted over a 45-year time horizon and adopted a Canadian public health system perspective. The populations considered were in line with the Health Canada indication and reimbursement request: patients with inadequate response to cDMARDS (cDMARDs-IR) and patients with inadequate response to bDMARDs (bDMARDs-IR). The manufacturer compared baricitinib as initial treatment as part of a treatment sequence, with a series of comparators, with the same follow-up sequence as baricitinib. The initial treatments that were compared were baricitinib, golimumab, abatacept iv, tofacitinib, sarilumab, tocilizumab, and the follow-up sequence alone. The clinical data were based on a manufacturer-provided NMA for both the cDMARDs-IR population and bDMARDs-IR population. The manufacturer's probabilistic base-case analyses indicated that for both cohorts of patients with moderate-to-severe RA, baricitinib sequence is extendedly dominated (i.e., has a higher incremental cost-utility ratio [ICUR] than the reference treatment [follow-up sequence alone] and next most cost-effective treatment [cDMARD-IR, tofacitinib; bDMARD-IR, tocilizumab]).

CADTH identified the following key limitations:

- The submitted model was unnecessarily complex and lacked transparency.
- The patient cohorts considered in the manufacturer's analysis were highly heterogeneous in terms of patient age and HAQ score.
- The manufacturer did not consider biosimilar comparators (e.g., infliximab, etanercept) as distinct treatments and assumed a blended comparator with the branded components (95% brand, 5% biosimilar).

The results of the CADTH reanalyses indicated that the patient cohort in the manufacturer's model, which contained individuals over a wide range of ages and initial disease severity, masked important insights into the cost-effectiveness of baricitinib and other bDMARDs for the treatment of RA. However, at a broader cohort level, the results of the CADTH reanalyses were generally consistent with the manufacturer's analysis. CADTH analyses identified that for both populations (cDMARD-IR and bDMARD-IR) with moderate-to-severe RA, baricitinib is dominated (i.e., costs more and provides fewer quality-adjusted life years [QALYs] than comparators) or extendedly dominated.

For patients with inadequate response to cDMARDs, a price reduction of more than 40% is required for baricitinib to achieve an ICUR below $50,000 per QALY compared with the most efficient treatment strategy (infliximab biosimilar). For patients with inadequate response to bDMARDs, a price reduction of 15% results in an ICUR of $34,890 per QALY gained for baricitinib compared with the most efficient treatment strategy (follow-up sequence alone).

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.

June 19, 2019 Meeting

Regrets

None

Conflicts of Interest

None