CADTH

CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**Upadacitinib (Rinvoq — AbbVie)**
Indication: For the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

## RECOMMENDATION

The CADTH Canadian Drug Expert Committee recommends that upadacitinib be reimbursed for use as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drugs for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), if the following conditions are met.

### Conditions for Reimbursement

**Initiation Criteria**
1. Adult patients with moderately to severely active RA on stable doses of disease-modifying anti-rheumatic drugs (DMARDs) who have had inadequate response or intolerance to methotrexate.
2. Upadacitinib should not be used in combination with other biologic DMARDs (bDMARDs) or Janus kinase inhibitors.

**Discontinuation Criteria**
1. Discontinue treatment if no response is observed by 12 weeks. A response to treatment is defined as an achievement of an American College of Rheumatology improvement criteria of at least 20%.

**Prescribing Conditions**
1. Patient should be under the care of a rheumatologist.
2. Daily dosage of upadacitinib should not exceed 15 mg.

**Pricing Conditions**
1. The drug plan cost of upadacitinib should not exceed the drug plan cost of treatment with the least costly bDMARD or targeted synthetic DMARD reimbursed for the treatment of moderate-to-severe RA.


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# UPADACITINIB (Rinvoq — AbbVie)

Indication: For the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Upadacitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that upadacitinib be reimbursed for use as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), if the following conditions are met.

## Conditions for Reimbursement

**Initiation Criteria**

1. Adult patients with moderately to severely active RA on stable doses of disease-modifying antirheumatic drugs (DMARDs) who have had inadequate response or intolerance to methotrexate.
2. Upadacitinib should not be used in combination with other biologic DMARDs (bDMARDs) or Janus kinase (JAK) inhibitors.

**Discontinuation Criteria**

1. Discontinue treatment if no response is observed 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).

**Prescribing Conditions**

1. Patient should be under the care of a rheumatologist.
2. Daily dosage of upadacitinib should not to exceed 15 mg.

**Pricing Conditions**

1. The drug plan cost of upadacitinib should not exceed the drug plan cost of treatment with the least costly bDMARD or targeted synthetic DMARD (tsDMARD) reimbursed for the treatment of moderate-to-severe RA.

## Reasons for the Recommendation

1. In three double-blind, randomized controlled trials (RCTs) (COMPARE, NEXT, and BEYOND), the percentage of patients achieving ACR20 at week 12 was statistically significantly higher in patients treated with upadacitinib compared with placebo: COMPARE (upadacitinib: 70.5% [95% confidence interval [CI], 67.0 to 74.0]; placebo: 36.4% [95% CI, 32.7 to 40.1]); NEXT (upadacitinib: 63.8% [95% CI, 57.5 to 70.1]; placebo: 35.7% [95% CI, 29.4 to 42.1]); BEYOND (upadacitinib: 64.6% [95% CI, 57.3 to 72.0]; placebo: 28.4% [95% CI, 21.6 to 35.2]). In one double-blind RCT (MONOTHERAPY), the percentage of patients achieving ACR20 at week 14 was statistically significantly higher in patients treated with upadacitinib compared with methotrexate (upadacitinib: 67.7% [95% CI, 61.5 to 74.0]; methotrexate: 41.2% [95% CI, 34.6 to 47.8]). In all four trials, the magnitude of improvement was statistically significantly greater on the Health Assessment Questionnaire – Disability Index (HAQ-DI) and on the Disease Activity Scale-28 and C-reactive protein (DAS28-CRP) in patients treated with upadacitinib compared with either placebo or methotrexate. Patients enrolled in the COMPARE trial received methotrexate background therapy, while patients enrolled in the NEXT and BEYOND trials received background therapy with any csDMARD.
2. In one double-blind, RCT (COMPARE), the percentage of patients achieving ACR50 at week 12 was statistically significantly higher in patients treated with upadacitinib compared with adalimumab (45.2% [95% CI, 41.3 to 49.0] versus 29.1% [95% CI, 24.1 to 34.0], respectively). In addition, upadacitinib was statistically superior to adalimumab on the HAQ-DI (least squares mean difference = –0.11 [95% CI, –0.184 to –0.036]), but this treatment difference was not clinically significant.
3. Direct comparative evidence for upadacitinib versus other bDMARDs is limited to adalimumab. Limitations associated with the sponsor's submitted indirect treatment comparison (ITC) did not permit any definitive conclusions regarding the comparative effectiveness of upadacitinib versus other bDMARDs or tsDMARDs used to treat moderate-to-severe RA in Canada. There is limited data to support a price premium for upadacitinib relative to the least costly treatment alternative.
4. At the submitted price, upadacitinib is not cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY). Given the uncertainty regarding the comparative effectiveness of upadacitinib versus other bDMARDs and

tsDMARDs, and the limitations of the cost-utility analysis model, there is insufficient evidence to justify a cost premium over the least expensive bDMARD or tsDMARD reimbursed for the treatment of moderate-to-severe RA.

## Discussion Points

1. Upadacitinib is the third JAK inhibitor marketed in Canada. The others are tofacitinib and baricitinib. There is no direct evidence to suggest that upadacitinib offers any clinical benefit over baricitinib or tofacitinib. The ITCs evaluated by CADTH did not establish significant differences between upadacitinib, baricitinib, or tofacitinib in terms of achieving ACR responses.
2. CDEC noted limitations associated with the sponsor-submitted ITC. [redacted].
3. CDEC noted that there is no evidence demonstrating the efficacy of upadacitinib in patients who have been previously treated with another JAK inhibitor. In all of the included trials, previous experience with JAK inhibitors was an exclusion criterion. This was considered an important evidence gap by CDEC given that upadacitinib is indicated for use in patients who have had an inadequate response or intolerance to methotrexate.

## Background

Upadacitinib is indicated for the treatment of moderate-to-severe active RA in adult patients who have had an inadequate response or intolerance to methotrexate. Upadacitinib is a JAK inhibitor and modulates the signalling pathway at the point of JAKs, preventing the phosphorylation and activation of signal transducers and activators of transcription pathways. It is available as orally administered extended-release tablets and the dosage recommended by Health Canada is 15 mg once daily, with or without food.

## Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of double-blind RCTs of upadacitinib, two ITCs, and a critique of the sponsor'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

Two patient group submissions were received for this review — a joint submission from the Canadian Arthritis Patient Alliance (CAPA) and the Arthritis Society (AS), and a submission from Arthritis Consumer Experts. In both cases, patient perspectives were obtained through online surveys. CAPA and AS, assisted by the sponsor, reached out to the patient community involved in the upadacitinib trials. CAPA and AS received a total of 51 responses, including one from a patient who was enrolled in one of the upadacitinib trials, while the Arthritis Consumer Experts outreach received input from six patients. The following is a summary of key input from the perspective of the patient groups:

- Patients reported that despite the wide range of currently available medications, they still have difficulty controlling 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 their families.
- Patients reported having to try multiple medications, or a combination of several, before finding one that works, and once they do find a therapy that works they may still eventually experience loss of efficacy and need to seek a new alternative. Patients also cited negative experiences with side effects as a major concern with existing therapies.
- The most common sentiment regarding upadacitinib was that, in addition to representing another option for RA, patients saw a potential for enhanced efficacy, specifically with respect to joint swelling and pain, leading to an improvement in quality of life. Ease of administration was also seen as a potential improvement with upadacitinib compared with infusions and injections, which were seen as painful and time consuming. One patient had experience with upadacitinib and reported positive experiences.

## Clinical Trials

The systematic review included five pivotal multinational double-blind RCTs: COMPARE, NEXT, BEYOND, MONOTHERAPY, and EARLY. Patients included in the EARLY study were treatment naive, which is beyond the Health Canada indication.

All of the other studies enrolled adults with RA whose symptoms were inadequately controlled with a DMARD. In COMPARE (N = 1,629) patients were inadequately controlled on methotrexate and were randomized (2:1:2) to upadacitinib 15 mg once daily, adalimumab 40 mg injection every other week, or placebo. In NEXT (N = 661) patients were inadequately controlled on any csDMARD (csDMARD inadequate responders [csDMARD-IR]) and were randomized to upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, or placebo. In BEYOND (N = 499) patients were inadequately controlled on a bDMARD (bDMARD inadequate responders [bDMARD-IR]) and were randomized to upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, or placebo. In MONOTHERAPY, patients had previous treatment with a csDMARD and were randomized to upadacitinib once daily 15 mg, once daily 30 mg, or methotrexate (to continue on prior stable dose). Patients enrolled in COMPARE received methotrexate background therapy, while patients enrolled in NEXT and BEYOND received background therapy with any csDMARD. Patients enrolled in MONOTHERAPY did not receive any background therapy.

The main limitation associated with the evidence reviewed was the lack of direct comparison against other existing bDMARDS (other than adalimumab) and JAK inhibitors.

## Outcomes

Outcomes were defined a priori in the CADTH systematic review protocol. Of these, the committee discussed the following: ACR responses, the HAQ-DI, the DAS28- CRP, and the modified total Sharp score (mTSS). The primary outcome in the COMPARE, NEXT, and BEYOND studies was the proportion of patients achieving an ACR20 response at 12 weeks; the primary outcome in MONOTHERAPY was ACR20 at 14 weeks.

- 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 (week 14 in MONOTHERAPY) in the DAS28-CRP was a secondary outcome of all of the included studies. DAS28-CRP is based on a 28-joint count that includes hands, wrists, elbows, shoulders, and knees. A DAS28 score indicates an absolute level of disease activity with a score of 5.1 or greater being considered high disease activity, while a DAS28 score lower than 3.2 indicates a low disease activity state and a DAS28 score lower than 2.6 indicates remission.
- The change from baseline to week 12 (week 14 in MONOTHERAPY) in HAQ-DI was a secondary outcome of all of the included studies. The full HAQ collects data on five generic patient-centred 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 important difference is 0.22; however, lower values have been reported.
- A change from baseline in the mTSS was a secondary radiographic outcome in COMPARE. The outcome was assessed centrally by two qualified physicians or radiologists who were blinded to the site number, subject number, treatment allocation, time sequence, and clinical response. The score includes 16 joints from the hands and wrists (graded from zero to five) and six joints from the feet (graded from zero to 10). The joint space narrowing score includes 15 areas from the hands and wrists (graded from zero to four) and six areas from the feet (also graded from zero to four). The maximum erosion score is 160 for hands and wrists and 120 for feet, while the maximum joint space narrowing score is 120 for hands and 48 for feet.

## Efficacy

The primary outcome in COMPARE of ACR20 at week 12 showed a response of 70.5% (95% CI, 67.0 to 74.0) in upadacitinib-treated patients and 36.4% (95% CI, 32.7 to 40.1) in placebo-treated patients, with a rate difference 34.1 (95% CI, 29.0 to 39.2). Also, in COMPARE, the initial outcome in the comparison against adalimumab of ACR50 at week 12 showed a response of 45.2% (95% CI, 41.3 to 49.0) in upadacitinib-treated patients and 29.1% (95% CI, 24.1 to 34.0) in adalimumab-treated patients, with a rate difference of 16.1 (95% CI, 9.9 to 22.3). The primary outcome in NEXT of ACR20 at week 12 was 63.8% (95% CI, 57.5 to 70.1) in upadacitinib-treated patients and 35.7% (95% CI, 29.4 to 42.1) in the placebo-treated patients, with a rate difference of 28.1 (95% CI, 19.1 to 37.0). In BEYOND, the primary outcome of ACR20 at week 12 was 64.6% (95% CI, 57.3 to 72.0) in upadacitinib-treated patients and 28.4% (95% CI, 21.6 to 35.2) in placebo-treated patients, with a rate difference of 36.2 (95% CI, 26.2 to 46.2). The primary outcome in MONOTHERAPY of ACR20 at week 14 showed a response rate of 67.7% (95% CI, 61.5 to 74.0) in upadacitinib-treated patients and 41.2% (95% CI, 34.6 to 47.8) in methotrexate-treated patients, with a rate difference of 26.5 (95% CI, 17.5 to 35.6).

The HAQ-DI was a secondary outcome in all of the studies. Results of the upadacitinib 15 mg group versus the placebo and methotrexate groups achieved a statistically significant difference greater than the estimated minimal important difference of 0.22 in all of the studies at week 12 (week 14 in MONOTHERAPY). Specifically, the mean difference between upadacitinib- and placebo-treated patients in COMPARE was –1.33 (95% CI, –1.47 to –1.19), in NEXT was –1.18 (95% CI, –1.420 to –0.939), and in BEYOND was –1.29 (95% CI, –1.574 to –1.008). The mean difference between upadacitinib- and methotrexate-treated patients in MONOTHERAPY was –1.08 (95% CI, –1.319 to –0.848). The mean difference between upadacitinib- and adalimumab-treated patients in COMPARE was –0.47 (95% CI, –0.638 to –0.295).

The DAS28-CRP was a secondary outcome in all studies. Results of the upadacitinib 15 mg group versus the placebo and methotrexate groups achieved a statistically significant mean difference in all of the studies. Specifically, the mean difference between upadacitinib- and placebo-treated patients in COMPARE was –0.31 (95% CI, –0.372, –0.253), in NEXT was –0.33 (95% CI, –0.432, –0.236), and in BEYOND was –0.22 (95% CI, –0.343, –0.100). The mean difference between upadacitinib- and methotrexate-treated patients in MONOTHERAPY was –0.33 (95% CI, –0.431 to –0.220). The mean difference between upadacitinib- and adalimumab-treated patients in COMPARE was –0.11 (95% CI, –0.184, –0.036); however, this result was outside the statistical testing hierarchy.

The mTSS was reported in COMPARE (week 24) as a secondary outcome, with a responder analysis where a responder was defined as having no change in mTSS. The mean difference was statistically significantly in favour of upadacitinib and, similarly, the response rate in upadacitinib-treated patients was statistically significantly higher than in placebo-treated patients (rate difference = 7.5 [95% CI, 3.0 to 12.1]).

## Harms (Safety)

In COMPARE, 64.2% of upadacitinib patients, 60.2% of adalimumab patients, and 53.2% of placebo patients experienced an adverse event. In MONOTHERAPY, the percentages were 47.5% in the upadacitinib group and 47.2% in the placebo group. In NEXT, the percentages were 56.6% in the upadacitinib group and 48.9% in the placebo group. In BEYOND, the percentages were 55.5% in the upadacitinib group and 56.2% in the placebo group. Respiratory tract infections were the most common adverse events in all of the included studies.

Serious adverse events (SAE) were generally less than 5% across the studies. In COMPARE, 3.7% of upadacitinib patients, 4.3% of adalimumab patients, and 2.9% of placebo patients experienced an SAE. In MONOTHERAPY, the percentages of patients who reported an SAE were 5.1% and 2.8% in the upadacitinib and methotrexate groups, respectively. In NEXT, the percentages of patients who reported an SAE were 4.1% and 2.3% in the upadacitinib and placebo groups, respectively. In BEYOND, the percentages were 4.9% in the upadacitinib group and 0% in the placebo group. No single SAE was most common across the included studies.

Based on the available data, there was a numerically higher incidence of developing a Herpes Zoster infection in the upadacitinib treatment groups when contrasted with the non-upadacitinib treatment groups. Overall, notable harms identified for this review did not show explicit imbalance between groups, with the exception of a numerically higher proportion of neutropenia in upadacitinib-

treated patients in COMPARE and BEYOND. Also, thromboembolic events were reported in 0.6% of all patients treated with upadacitinib in the long-term study.

## Indirect Treatment Comparisons

CADTH reviewed two ITC reports, one submitted by the sponsor and one identified in the literature search conducted by CADTH. Both utilized a Bayesian network meta-analysis approach. [redacted]. The published ITC by Song et al. (and identified by CADTH) only compared upadacitinib to tofacitinib.

In the csDMARD-experienced population, [redacted].

Song et al. reported that upadacitinib had a higher odds ratio of achieving the efficacy outcome compared with tofacitinib. However, the CrI was wide and included the null (odds ratio = 1.52 [95% CrI, 0.64 to 3.26]).

There are several limitations that increase the uncertainty in the results provided in the ITCs. [redacted]. The ITC by Song et al. did not provide sufficient information regarding the included studies' characteristics, baseline demographics of enrolled patients, methods of combining different routes of administration, and different definitions of inadequate responders and potential outcomes. An informed judgment of potential clinical or methodological heterogeneity cannot be made in the absence of this information.

## Cost and Cost-Effectiveness

Upadacitinib is available as a 15 mg tablet, at a submitted price of $48.68 per tablet. The recommended starting dose as monotherapy or in combination with a csDMARD is 15 mg daily, at an annual treatment cost of $17,770 per patient.

The sponsor submitted a cost-utility analysis considering upadacitinib as initial treatment for moderate-to-severe RA following an inadequate response to either a csDMARD or bDMARD. Comparators included csDMARDs, bDMARDs, and other tsDMARDs. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a five-year time horizon. The pharmacoeconomic submission was based on a Markov model that comprised four main health states, three based on levels of ACR response and one in which patients did not achieve minimum response. Patients with an inadequate response or who discontinued treatment due to SAEs could receive subsequent treatment, and subsequent failure patients received best supportive care (BSC). A sponsor-commissioned ITC informed the comparative ACR response at weeks 12 and 24. In the sponsor's base-case analysis, upadacitinib plus csDMARD was the preferred treatment option if the decision-maker's WTP is more than $107,659 per QALY in the csDMARD-IR population; upadacitinib monotherapy was extendedly dominated through etanercept plus csDMARD and upadacitinib plus csDMARD. In the bDMARD-IR population, upadacitinib plus csDMARD was the preferred treatment option if the decision-maker's WTP is between $104,193 and $303,516 per QALY.

The following key limitations were identified:

- There was uncertainty associated with the comparative efficacy estimates from the ITC submitted by the sponsor, with high statistical variation within the bDMARD-IR population.

- The simplifying assumption of subsequent treatments does not reflect Canadian clinical practice and clinical expert feedback indicated that the majority of patients would receive more than two bDMARDs or tsDMARDs prior to receiving supportive care.
- The sponsor overestimated the cost of BSC, with the assumption that patients would receive a prior bDMARD or tsDMARD that achieved the "best treatment effect," which does not align with clinical practice.

The CADTH base-case analysis reflected changes to the following parameters: corrections were applied to the base drug costs, mortality data, and resource use values; RA-specific mortality was incorporated; costs of csDMARD were used for BSC; treatment administration costs were removed; equal efficacy for subsequent treatments was assumed; nonresponders and patients discontinuing treatment returned to baseline HAQ; and a non-linear mapping equation for HAQ to the EuroQol 5-Dimensions questionnaire was applied.

The CADTH reanalysis results aligned with the sponsor's base-case results, indicating that upadacitinib monotherapy, or in combination with a csDMARD, is not a cost-effective treatment at conventionally accepted WTP thresholds. Price reductions of 50% to 60% (csDMARD-IR population) and 60% to 70% (bDMARD-IR population) are required for upadacitinib plus csDMARD to be considered cost-effective at a WTP of $50,000 per QALY. If csDMARD monotherapy is excluded as a comparator, a 30% to 35% price reduction is required for upadacitinib monotherapy and upadacitinib plus csDMARD to be cost-effective in the csDMARD-IR population, and a 5% reduction is required for upadacitinib plus csDMARD in the bDMARD-IR population.

Several limitations were identified that could not be addressed by CADTH, most notably the inability to explore the cost-effectiveness according to moderate or severe patients with RA and longer-term (more than five years) time horizon. The cost-effectiveness of upadacitinib should be considered within the context of these limitations.

## CDEC Members

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

## November 20, 2019 Meeting

## Regrets

None

## Conflicts of Interest

None