CADTH

CADTH Reimbursement Recommendation

Upadacitinib (Rinvoq)

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

Sponsor: AbbVie Corporation

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Rinvoq?

CADTH recommends that Rinvoq should be reimbursed by public drug plans for the treatment of active psoriatic arthritis (PsA) if certain conditions are met.

What Are the Conditions for Reimbursement?

Rinvoq should only be reimbursed if it is prescribed by a rheumatologist or a clinician who has experience treating adult patients with active PsA and if it does not cost more than other biologic disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs).

Which Patients Are Eligible for Coverage?

Rinvoq should only be covered to treat adult patients with active PsA who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs) in a similar way to other bDMARDs currently reimbursed by public drug plans.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Rinvoq improves PsA symptoms compared to treatment with placebo.
- Rinvoq may meet some of the needs that are important to patients, including reducing joint pain, clearing psoriasis, and improving their health-related quality of life.
- There is no evidence to suggest treatment with Rinvoq is more effective than other reimbursed therapies used to treat adult patients with active PsA. Therefore, Rinvoq should be priced no higher than the least costly bDMARD or tsDMARDs to ensure cost-effectiveness.
- Based on public list prices for all therapies reimbursed by public drug plans, the 3-year budget impact may range from a savings of approximately $2.5 million to an incremental cost of approximately $3.1 million depending upon biosimilar pricing and use. Additional uncertainty in the estimates was identified due to limitations with the sponsor's model that could not be addressed by CADTH.

Additional Information

What Is PsA?

PsA is a form of arthritis. People with PsA have skin lesions associated with psoriasis, and often have inflamed joints, which may include the large joints of the arms and legs, the smaller joints in the fingers and toes, and spine. Pain and stiffness of the affected joints are the most common symptoms, and many patients also experience fatigue. The prevalence of PsA varies; it is estimated to be 1 to 2 per 1,000 in the general population.

Unmet Needs in PsA

Although many treatments are approved in Canada to treat active PsA, some patients may not respond to these treatments. Other treatment options are needed for these patients.

How Much Does Rinvoq Cost?

Treatment with Rinvoq is expected to cost approximately $17,768 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that upadacitinib should be reimbursed as monotherapy or in combination with methotrexate for the treatment of adults with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 2 double-blind, randomized controlled trials in adults with moderate-to-severe active PsA who had an insufficient response or intolerance to a non-biologic DMARD (bDMARD) and who were bDMARD naive (SELECT-PsA 1 trial) or who had insufficient response or intolerance to a bDMARD (SELECT-PsA 2 trial), upadacitinib 15 mg once daily was associated with statistically significant and clinically meaningful improvements compared with placebo in the proportion of patients achieving at least a 20% improvement in American College of Rheumatology response criteria (ACR20) at week 12 (the primary efficacy outcome). The difference between the upadacitinib 15 mg group and the placebo treatment group was 34.5% (95% confidence interval [CI], 28.2% to 40.7%; P < 0.0001) in the SELECT-PsA 1 trial and 32.8% (95% CI, 24.0% to 41.6%; P < 0.0001) in the SELECT-PsA 2 trial. In bDMARD-naive patients, upadacitinib was noninferior to adalimumab 40 mg subcutaneous (SC) every other week for the ACR20 response at week 12. The efficacy of upadacitinib compared with adalimumab in bDMARD-experienced patients is unknown. In both studies, upadacitinib 15 mg was associated with statistically significant improvements compared with placebo for numerous clinically relevant manifestations of PsA, including function and disability as measured with the Health Assessment Questionnaire – Disability Index (HAQ-DI), PsA symptoms as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), health-related quality of life (HRQoL) as measured by the Physical Component Summary (PCS) component of the Short Form (36) Health Survey (SF-36), skin disease as measured by the Psoriasis Area and Severity Index (PASI) and static Investigator Global Assessment (sIGA), and other measures of clinical response or disease control such as minimal disease activity (MDA).

Patient input received for this review articulated that there is a need for new PsA treatment alternatives that are effective in reducing PsA symptoms, including joint pain, clearing psoriasis, and improving HRQoL. Based on the results from the SELECT-PsA 1 and SELECT-PsA 2 studies, upadacitinib appears to address some of these important outcomes valued by patients.

Direct comparative evidence for upadacitinib versus bDMARDs (other than versus adalimumab) or targeted synthetic DMARDs (tsDMARDs) was not identified. One sponsor-submitted indirect treatment comparison (ITC) compared upadacitinib to bDMARDs or tsDMARDs. Results from the ITC suggest that upadacitinib does not show a consistent or distinct difference in efficacy, as measured by ACR, PASI, Psoriatic Arthritis Response Criteria (PsARC), or HAQ-DI, between bDMARDs and tsDMARDs for both bDMARD-naive and bDMARD-experienced patients. There is uncertainty about the ITC results due to the inherent heterogeneity across trials in the networks.

Using the sponsor-submitted price for upadacitinib and publicly listed prices for all other drug costs, upadacitinib was more costly compared with several relevant comparator treatments for adults with active PsA who have had an inadequate response to previous DMARDs or for whom DMARDs are not tolerated or contraindicated. The Committee considered that there is insufficient evidence to justify a cost premium over the least expensive bDMARD or tsDMARDs reimbursed for the treatment of adult patients with PsA.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Eligibility for upadacitinib should be based on the criteria used by each of the public drug plans for reimbursement of bDMARDs for the treatment of active PsA.	There is no direct evidence that upadacitinib is clinically superior or inferior to other biologic treatments currently reimbursed for the treatment of active PsA. In bDMARD-naive patients (SELECT-PsA 1 study), upadacitinib 15 mg orally once daily was noninferior to adalimumab 40 mg SC every other week in achievement of ACR20 response at week 12.
Renewal	
2. Upadacitinib should be renewed in a similar manner to other bDMARDs currently reimbursed for the treatment of adult patients with active PsA.	There is no evidence that upadacitinib should be held to a different standard than other reimbursed options when considering renewal.
Prescribing	
3. Patient should be under the care of a rheumatologist or a clinician who has experience treating adult patients with active PsA.	Accurate diagnosis and follow-up of patients with active PsA are important to ensure that upadacitinib is prescribed to the most appropriate patients. In addition, there are several bDMARD and tsDMARD treatment options that may be considered when selecting the most appropriate therapy for patients; these are best determined by a rheumatologist or clinician who is familiar with this complex treatment paradigm.
4. Upadacitinib should not be reimbursed when used in combination with bDMARDS or other JAK-inhibitor treatments for active PsA.	There is no evidence to determine the effects of upadacitinib when used in combination with bDMARDs or other JAK inhibitors in patients with active PsA.
Pricing	
5. The cost of upadacitinib should not exceed the drug program cost of treatment with the least costly bDMARD or tsDMARD reimbursed for the treatment of active PsA.	Upadacitinib did not demonstrate improved efficacy or harms compared to bDMARDs based on direct evidence (SELECT-PsA 1 study). Indirect evidence for upadacitinib compared with other treatments in patients who were bDMARD-naive and bDMARD-experienced were associated with several limitations. Based on the totality of evidence, CADTH noted that upadacitinib does not show any difference in efficacy, in terms of PsARC, PASI, HAQ-DI change, and ACR, compared with bDMARDs and tsDMARDs.

ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire – Disability Index; JAK = Janus kinase; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Implementation Guidance

1. Upadacitinib may be used as monotherapy or in combination with methotrexate. Approximately 80% of patients in the SELECT-PsA 1 study and 50% of patients in the SELECT-PsA 2 study received concomitant non-bDMARDs (mostly methotrexate); a subgroup analysis found consistent treatment effects regardless of concomitant non-bDMARD use.

2. CDEC noted that there is no evidence demonstrating the efficacy of upadacitinib in patients who have been previously treated with another Janus kinase (JAK) inhibitor. This was considered an important evidence gap by CDEC. The clinical expert noted that patients who do not respond to tofacitinib treatment or who were previously treated with tofacitinib for PsA may be treated with upadacitinib but that patients responding to tofacitinib should not be switched to upadacitinib because their subsequent response is unknown. The clinical expert also noted that patients who are successfully treated with biologic therapy should not switch treatment to upadacitinib just because it offers an oral option; however, patients who failed previous treatment with a bDMARDs should be eligible to switch to upadacitinib.

Discussion Points

- CDEC noted that the only long-term comparative evidence available for upadacitinib was compared with adalimumab in bDMARD-naive patients; however, only descriptive statistics were available. Except for adalimumab, there is no direct long-term evidence comparing upadacitinib to other bDMARDs or tsDMARDs available in Canada. In addition, the sponsor-submitted ITC used study results collected over a relatively short duration. Because PsA is a chronic condition that requires lifelong treatment, there is uncertainty regarding the long-term effectiveness and safety of upadacitinib over other currently available bDMARDs or tsDMARDs for the treatment of active PsA.

- Patient groups indicated the need for a treatment that would improve HRQoL with minimal adverse effects. The only comparative evidence available is for upadacitinib compared with adalimumab in bDMARD-naive patients, and most HRQoL outcomes were outside of the statistical testing hierarchy. The sponsor-submitted ITC did not assess comparative HRQoL or safety. Hence, there is no evidence that upadacitinib would improve HRQoL or have a lower rate of adverse events (AEs) compared with other currently available bDMARDs or tsDMARDs for the treatment of active PsA.

Background

Upadacitinib has a Health Canada indication for the treatment of adults with active PsA who have had an inadequate response or intolerance to methotrexate or other DMARDs. Upadacitinib may be used as monotherapy or in combination with methotrexate. Upadacitinib is a JAK inhibitor, which modulates the signalling pathway at the point of the JAKs, preventing the phosphorylation and activation of signal transducers and activators of transcription pathways. It is available as orally administered extended-release tablets; the Health Canada–approved dose is 15 mg orally once daily.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a systematic review that included 2 phase III randomized controlled trials in adult patients with an established diagnosis of moderate-to-severe active PsA who had been previously treated with a DMARD
- patients' perspectives gathered by patient groups, including the Arthritis Consumer Experts (ACE), the Canadian Spondylitis Association (CSA), the Canadian Association of Psoriasis Patients (CAPP) partnering with the Canadian Psoriasis Network (CPN), and the Canadian Arthritis Patient Alliance (CAPA) partnering with the Arthritis Society
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a clinical specialist with expertise in diagnosing and treating patients with PsA
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Four inputs were submitted for this review representing 6 different patient groups: ACE, CSA, CAPP partnering with CPN, and the CAPA partnering with the Arthritis Society. Patient perspectives were obtained from surveys. The following is a summary of key input from the perspective of the patient group(s):

- Survey respondents emphasized pain, stiffness, lack of mobility, and fatigue, which impact their activities of daily living, their family lives, and their ability to work and maintain certain hobbies. The impact of PsA extends to others within a person's support circle, including caregivers such as spouses, partners, or children, who may have to take on additional roles or tasks to support the person living with PsA.
- Patients living with psoriatic disease often try a succession of treatments throughout their lives. Responses to medications can vary significantly between individuals, and treatments that are initially effective can become less effective over time. As a result, patients need several treatment options to effectively manage their disease throughout their lives.
- Outcomes that were identified as important to patients with PsA included a reduction in symptoms, particularly pain and fatigue; treatments that are effective for psoriasis as well as PsA symptoms; increased mobility; improved quality of life (including ability to work and be productive at work, ability to carry out activities of daily living, ability to effectively carry out parenting tasks and other important social roles); reduced infection rates; route of drug administration (oral versus infusion versus self-injections); and affordability of the medication.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert consulted by CADTH for this review identified an unmet need in the treatment of psoriatic disease is that some patients may not respond to any treatment, and

only a minority achieve MDA. In the treatment of PsA, numerous domains of disease activity need to be addressed, which might not be accomplished by a single agent. In patients who do not respond or become refractory to treatment, a switch to a treatment with a different mechanism of action will be necessary.

The clinical expert indicated that any patient with peripheral joint and skin disease who does not respond to conventional synthetic disease-modifying antirheumatic drug would be eligible for upadacitinib, barring any contraindications. Tumour necrosis factor (TNF) inhibitors and interleukin-17 (IL-17) inhibitors will generally be prescribed before upadacitinib. However, the clinical expert noted that, as clinicians become more experienced with upadacitinib and with confirmation of the long-term safety, upadacitinib might become the first-line treatment for PsA. The caveat with this assumption is that longer-term observation in patients on upadacitinib will be needed to confirm the durability of benefit and safety. The clinical expert also identified the oral route of upadacitinib as an advantage, with the improved convenience over SC injections or IV infusions, which would be expected to enhance treatment adherence. It is expected that the benefits from a JAK inhibitor will be apparent sooner than with TNF inhibitors, and a lack of response and/or increased side effects will result in the decision to discontinue treatment.

According to the clinical expert, in clinical practice, the swollen joint count is the most likely measure to assess response, with a reduction in joint count reflecting meaningful response. Other clinically meaningful responses may be measured using the achievement of MDA or patient-reported outcomes.

Drug Program Input

Input was obtained from the jurisdictions participating in CADTH reimbursement reviews. The following were identified as key factors that could impact the implementation:

- The place in therapy of upadacitinib relative to currently available treatments for PsA.
  - The clinical expert indicated that the place in therapy of upadacitinib would be the same as that of the bDMARDs.
- The significance of potential AEs associated with JAK inhibitors.
  - The clinical expert does not expect that upadacitinib would have an impact on cardiovascular morbidity and mortality. Patients should be treated for their lipid abnormalities according to their risk and the standard of care; however, the full effect of upadacitinib on cardiovascular morbidity and mortality still need to be assessed.
- The expected dose of upadacitinib used and any potential for dose escalation.
  - Due to safety concerns of serious infection and herpes zoster, which increased with the upadacitinib 30 mg dose in comparison with the upadacitinib 15 mg dose, the clinical expert indicated that clinicians would be cautious about dose escalation. The clinical expert also stated that it is not expected that dose escalation beyond 15 mg of upadacitinib once daily would happen in the clinical practice of managing patients with PsA.

Clinical Evidence

Clinical Trials

Description of Studies

Two multi-centre, phase III, randomized, double-blind, placebo-controlled trials, SELECT-PsA 1 and SELECT-PsA 2, met the inclusion criteria for this review. Both SELECT studies enrolled adult patients with an established diagnosis of moderate-to-severe active PsA who had been previously treated with a DMARD. The SELECT-PsA 1 study included patients who had an insufficient response or intolerance to a non-bDMARD, whereas the SELECT-PsA 2 study included patients who had an insufficient response or intolerance to a bDMARD. Both trials investigated 2 doses of oral upadacitinib: 15 mg once daily and 30 mg once daily. However, to align with the Health Canada−recommended dosage, only results for the upadacitinib 15 mg once daily dose are presented in this review.

Efficacy and safety of upadacitinib was compared with placebo in both studies; the SELECT-PsA 1 study also included adalimumab as an active comparator. Both studies consisted of 2 periods, and at the end of week 24 in period 1, all patients on placebo were switched to upadacitinib. In the SELECT-PsA 1 study, period 1 consisted of 56 weeks in duration and included a 24-week double-blind placebo and active comparator-controlled period followed by 32 weeks of blinded active comparator-controlled treatment. The SELECT-PsA 2 study also consisted of a period 1 that was 56 weeks in duration and included 24 weeks of a double-blinded placebo-controlled phase followed by 32 weeks of a non-comparative treatment phase. Period 2 was an ongoing open-label, long-term treatment extension of up to approximately 5 years for the SELECT-PsA 1 study and 3 years for the SELECT-PsA 2 study.

In the SELECT-PsA 1 study (N = 1,705), eligible participants were randomized at a 2:2:2:1:1 ratio to 1 of 5 treatment groups: upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, adalimumab 40 mg SC every other week, and placebo followed by upadacitinib 15 mg once daily or placebo followed by upadacitinib 30 mg once daily. Randomization was stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, presence of dactylitis, and presence of enthesitis. Patients enrolled into SELECT-PsA 2 (N = 642), were randomized in a 2:2:1:1 ratio to 1 of 4 treatment groups similar to the SELECT-PsA 1 study, but without the adalimumab treatment group: upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, and placebo followed by either upadacitinib 15 mg once daily or upadacitinib 30 mg once daily. Randomization was stratified by extent of psoriasis, current use of at least 1 DMARD, and number of prior failed bDMARDs (1 versus > 1). Patients were permitted to continue their stable background non-bDMARD therapy, which was methotrexate for the majority of patients. Both studies had an appropriate randomization strategy; treatment groups within each study were generally well-balanced. Compared with the SELECT-PsA 1 study, the patients enrolled in the SELECT-PsA 2 study had PsA for longer with more significant disease.

The primary end point for both the SELECT-PsA 1 and SELECT-PsA 2 studies was the proportion of patients who achieved 20% ACR20 response, defined as an improvement of at least 20% in both swollen and tender joint counts and at least 3 of 5 additional disease criteria at week 12. The primary and major secondary efficacy outcomes were assessed using a hierarchical testing procedure to control the overall type I error rate. The multiplicity-adjusted testing hierarchy included the primary end point plus 14 ranked key secondary end points in the SELECT-PsA 1 study, and 7 ranked key secondary end points in the SELECT-PsA 2 study.

Several additional end points that were not part of the multiplicity-adjusted analyses but were identified in the CADTH systematic review protocol are also discussed in this report.

Efficacy Results

Clinical Responses in PsA Symptoms

Clinical response in PsA symptoms or overall disease activity were measured using ACR 20, MDA, and modified PsARC. In the SELECT-PsA 1 study, 70.6% and 36.2% of patients treated with upadacitinib 15 mg and placebo, respectively, achieved ACR20 response. The difference between the upadacitinib 15 mg group and placebo treatment group was 34.5% (95% CI, 28.2% to 40.7%; P < 0.0001), which was clinically relevant and statistically significant in favour of upadacitinib 15 mg. In the SELECT-PsA 2 study, 56.9% and 24.1% of patients treated with upadacitinib 15 mg and placebo, respectively, achieved ACR20 response. The difference between the upadacitinib 15 mg group and placebo treatment group was 32.8% (95% CI, 24.0% to 41.6%; P < 0.0001), which was clinically relevant and statistically significant in favour of upadacitinib 15 mg. In the SELECT-PsA 1 study, results of the pre-specified subgroup analyses by current use of non-bDMARDs, number of prior non-bDMARDs (SELECT-PsA 1 study), and number of prior failed bDMARDs (SELECT-PsA 2 study) were consistent with results from the overall population for the primary end point of ACR20 response at week 12; however, these analyses were not included in the hierarchical statistical analysis and should be interpreted with caution. The clinical expert consulted for this review noted that the differences in ACR20 responses compared with placebo were clinically meaningful.

In the SELECT-PsA 1 study, the proportion of patients achieving ACR20 at week 12 with upadacitinib treatment compared with adalimumab was tested for non-inferiority and superiority as key secondary end points. ACR20 response was achieved by 70.6% in the upadacitinib 15 mg group and by 65.0% of patients in the adalimumab group, the difference between the upadacitinib 15 mg group and adalimumab treatment group was 5.6% (95% CI, −0.6% to 11.8%). The preservation of adalimumab effect for ACR20 response rate, calculated as (upadacitinib − placebo) ÷ (adalimumab − placebo), was 119.4% (95% CI, 98.0% to 147.9%); the lower bound of the 95% CI had exceeded the pre-specified non-inferiority threshold of at least 50% of the placebo-subtracted adalimumab effect, indicating that upadacitinib 15 mg daily was noninferior to adalimumab 40 mg every other week. In the subsequent testing of superiority, upadacitinib 15 mg was not found to be superior compared with adalimumab 40 mg because it did not meet the statistical significance for superiority.

For clinical responses measured with the MDA criteria, patients treated with upadacitinib 15 mg had higher response rates compared with placebo at week 24 in both the SELECT-PsA 1 study (36.6% for upadacitinib 15 mg and 12.3% for placebo) and the SELECT-PsA 2 study (25.1% for upadacitinib 15 mg and 2.8% for placebo). The between-group differences were 24.3% (95% CI, 18.8 to 29.8%; P = 0.0004) in the SELECT-PsA 1 trial and 22.3% (95% CI, 16.0% to 28.6%; P < 0.0001) in the SELECT-PsA 2 trial. The between-group differences were statistically significant in favour of upadacitinib 15 mg in both trials.

For modified PsARC response at week 24, a higher proportion of patients treated with upadacitinib achieved a response compared with patients randomized to adalimumab or placebo in both studies (SELECT-PsA 1: 83.7% for upadacitinib 15 mg, 76.6% for adalimumab 40 mg, and 59.3% for placebo; SELECT-PsA 2: 68.2% for upadacitinib 15 mg and 36.3% for placebo). In the SELECT-PsA 1 study, the response rate difference between the upadacitinib and adalimumab groups was 7.0% (95% CI, 1.7% to 12.3%), whereas the difference between upadacitinib and placebo was 24.3% (95% CI, 18.5% to 30.2%). In the SELECT-PsA 2 study,

the difference between upadacitinib and placebo was 31.9% (95% CI, 22.9% to 40.9%). These analyses were not included in the hierarchical statistical analysis.

Measurement of Function and Disability

The improvement in physical function at week 12, as measured with the HAQ-DI, was statistically significant. The change in scores from baseline in upadacitinib 15 mg and placebo were −0.42 and −0.14, respectively, in the SELECT-PsA 1 study, and −0.30 and −0.10, respectively, in the SELECT-PsA 2 study. The differences in change from baseline between upadacitinib 15 mg and placebo were −0.28 (95% CI, −0.35 to −0.22; P < 0.0001) in the SELECT-PsA 1 study and −0.21 (95% CI, −0.30 to −0.12; P < 0.0001) in the SELECT-PsA 2 study. In both studies, the between-group differences between upadacitinib and placebo in the improvement of HAQ-DI score did not exceed the estimated minimally important difference (MID) found in the literature for HAQ-DI of 0.35. However, in the SELECT-PsA 1 study, the proportion of patients who achieved a clinically meaningful improvement in HAQ-DI at week 12 was 33.4%, 47.2%, and 57.9% in the placebo, adalimumab 40 mg, and upadacitinib 15 mg treatment groups, respectively, whereas in the SELECT-PsA 2 study, the proportion of patients who achieved a clinically meaningful improvement in HAQ-DI at week 12 was 27.2% and 44.6% in the placebo and upadacitinib 15 mg treatment groups, respectively.

Work productivity was measured by the Work Productivity and Activity Impairment (WPAI) questionnaire in some study participants in both studies. Numerically greater reductions in work or activity impairment due to disease were observed for the upadacitinib 15 mg group compared with the placebo group at week 24. Although it appears the suggested MID was achieved by patients in the upadacitinib group in the SELECT-PsA 1 study for improvement in presenteeism (≥ 20%) and activity impairment (≥ 20%), the between-group differences in change from baseline with upadacitinib compared with placebo or adalimumab did not exceed this threshold. The least squares (LS) mean difference in the change in scores between upadacitinib and adalimumab was −2.5 (95% CI, −6.2 to 1.2), whereas the LS mean difference between upadacitinib and placebo was −13.4 (95% CI, −17.1 to −9.7) in the SELECT-PsA 1 study and −12.2 (95% CI, −18.8 to −5.6) in the SELECT-PsA 2 study. With the smaller number of patients included in the analysis, and lack of a confirmed MID for the WPAI instrument, it remains unclear whether differences were clinically meaningful. This was identified as an important outcome by the patient groups; however, in both the SELECT-PsA 1 and SELECT-PsA 2 studies, it was an exploratory variable and was not included in the multiplicity-controlled analyses.

Measurement of PsA Symptoms

PsA symptoms such as fatigue and pain were reported in both studies. A statistically greater improvement in fatigue from baseline, measured using FACIT-F, was seen at week 12 with upadacitinib 15 mg compared with placebo in both studies. The mean changes from baseline were 6.3 for upadacitinib 15 mg and 2.8 for placebo in the SELECT-PsA 1 study (between-group difference of 3.5; 95% CI, 2.4 to 4.7; P = 0.0004), and 5.0 for upadacitinib 15 mg and 1.3 for placebo in the SELECT-PsA 2 study (between-group difference of 3.7; 95% CI, 2.0 to 5.4; P < 0.0001). The between-group difference in the improvement in FACIT-F score at week 12 exceeded the estimated MID (3.1 points) in both studies. The impact of upadacitinib on pain is uncertain because this end point was not part of the hierarchical analysis, and no MID was identified for the Patient's Assessment of Pain Numeric Rating Scale (NRS) in patients with PsA.

Health-Related Quality of Life

HRQoL was measured by SF-36 and EQ-5D-5L in the SELECT-PsA 1 and SELECT-PsA 2 studies. Only the PCS component of the SF-36 was part of the multiplicity-adjusted testing hierarchy in the SELECT studies; the difference between the 2 groups was statistically significant. In the SELECT-PsA 1 study, the difference in mean change from baseline for upadacitinib 15 mg versus placebo was 4.67 (95% CI, 3.67 to 5.67; P = 0.0004) in favour of upadacitinib 15 mg; in the SELECT-PsA 2 study, the difference in mean change from baseline for upadacitinib 15 mg versus placebo was 3.52 (95% CI, 2.07 to 4.98; P < 0.0001) in favour of upadacitinib 15 mg. For the Mental Component Summary (MCS), a numerically greater improvement from baseline was seen for upadacitinib compared with placebo in both trials; the difference in mean change from baseline between the 2 treatment groups was 1.70 (95% CI, 0.58 to 2.82) in the SELECT-PsA 1 study and 2.98 (95% CI, 1.44 to 4.52) in the SELECT-PsA 2 study. The results from the EQ-5D-5L suggest that there were greater improvements in the utility index and the visual analogue scale (VAS) scores from baseline to week 24 in the upadacitinib treatment group compared to patients randomized to placebo in both studies, as well as adalimumab in the SELECT-PsA 1 study. For the utility index, the difference in mean change from baseline between upadacitinib and adalimumab was 0.03 (95% CI, 0.00 to 0.05), whereas the difference in mean change from baseline between upadacitinib and placebo was 0.09 (95% CI, 0.06 to 0.11) in the SELECT-PsA 1 study and 0.10 (95% CI, 0.06 to 0.14) in the SELECT-PsA 2 study. For the VAS, the difference in mean change from baseline between upadacitinib and adalimumab was 2.8 (95% CI, 0.0 to 5.6), whereas the difference in mean change from baseline between upadacitinib and placebo was 10.9 (95% CI, 8.0 to 13.7) in the SELECT-PsA 1 study and 6.8 (95% CI, 2.5 to 11.1) in the SELECT-PsA 2 study. For the comparison of upadacitinib to placebo in both the SELECT-PsA 1 and SELECT-PsA 2 studies, the mean between-group differences in the EQ-5D-5L utility index reached the MID threshold identified in the literature for the general Canadian population (summarized mean = 0.056; SD = 0.011). These results suggested that treatment with upadacitinib 15 mg was associated with improved HRQoL. Although HRQoL was identified as an important outcome by the patient groups, the outcome measures of EQ-5D-5L and MCS of SF-36 were not part of the hierarchical analysis plan and were not adjusted for multiple comparisons; therefore, the results should be interpreted with caution due to the risk of inflated type I error.

Measurement of Skin Disease

The extent and severity of skin disease was measured in both studies using PASI, sIGA, and Self-Assessment of Psoriasis Symptoms (SAPS). Only patients with psoriasis involving a 3% or greater BSA baseline had a PASI assessment. In the SELECT-PsA 1 study, the proportion of patients achieving PASI 75 response in the upadacitinib 15 mg treatment group was 62.6% compared to 21.3% in the placebo treatment group; the difference between the upadacitinib 15 mg group and placebo treatment group was 41.3% (95% CI, 32.8% to 49.8%; P < 0.0001), which was statistically significant in favour of upadacitinib 15 mg. In the SELECT-PsA 2 study, the proportion of patients achieving PASI 75 response in the upadacitinib treatment group was 52.3% compared with 16.0% in the placebo treatment group, and the difference between the upadacitinib 15 mg group and placebo treatment group was 36.3% (95% CI, 25.6% to 46.9%; P < 0.001), which was statistically significant in favour of upadacitinib 15 mg. The clinical expert consulted for this review indicated that the between-group differences in PASI 75 were considered clinically relevant, although the true effect should be derived from separate studies that are specifically designed for patients with skin disease.

Only patients with a sIGA score of 2 or greater at baseline, and at least a 2-point improvement from baseline at week 16, were included in the assessment. In both the SELECT-PsA 1 and

SELECT-PsA 2 studies, a statistically significant difference in the proportion of patients achieving a response (sIGA of psoriasis score of 0 or 1) was seen in favour of upadacitinib. At week 16, the proportion of responders were 41.9% for upadacitinib 15 mg and 10.9% for placebo (between-group difference = 31.1%; 95% CI, 24.7% to 37.5%; P < 0.0001) in the SELECT-PsA 1 study and 36.8% for upadacitinib 15 mg and 9.2% for placebo (between-group difference = 27.6%; 95% CI, 19.2% to 36.1%; P < 0.0001) in the SELECT-PsA 2 study.

A greater reduction in SAPS score from baseline was reported for patients in the upadacitinib group compared with placebo at week 16. In the SELECT-PsA 1 study, the difference in LS mean change from baseline between upadacitinib and placebo was −17.1 (95% CI, −19.6 to −14.6) for upadacitinib 15 mg versus placebo. Testing for superiority of upadacitinib compared with placebo was part of the multiplicity-adjusted analyses in the SELECT-PsA 1 study; however, it was ranked after the hierarchical analysis failed and stopped so no appropriate statistical comparisons can be made. In the SELECT-PsA 2 study, the difference between groups in the LS mean change from baseline in SAPS scores was statistically significant, favouring upadacitinib compared with placebo (−22.9 [95% CI, −27.4 to −18.4], P < 0.0001).

Measurement of Other Musculoskeletal Disease

The impact of treatment on musculoskeletal disease was assessed by measuring resolution of enthesitis (with the Leeds Enthesitis Index [LEI]), resolution of dactylitis (with the Leeds Dactylitis Index [LDI]) and change in axial disease using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). For patients with enthesitis at baseline, resolution of enthesitis (LEI = 0) was achieved by a statistically significantly higher proportion of patients in the upadacitinib 15 mg treatment group (53.7%) compared with the placebo group (32.4%) at week 24 in the SELECT-PsA 1 study (between-group difference = 21.3%; 95% CI, 13.0 to 29.7; P = 0.0004). In the SELECT-PsA 2 study, a numerically higher proportion of patients in the upadacitinib 15 mg treatment group achieved resolution of enthesitis at week 24 compared with patients in the placebo group, with a difference of 27.6% (95% CI, 17.3 to 37.8); however, this end point was not part of the multiplicity-controlled analyses in the SELECT-PsA 2 study. Because there is a risk of inflated type I error, no appropriate statistical comparisons can be made. Resolution of dactylitis (LDI = 0) was achieved by a numerically higher proportion of patients in the upadacitinib group compared with the placebo group at week 24 in both trials. The difference between the 2 treatment groups was 36.8% (95% CI, 25.7 to 47.9) in the SELECT-PsA 1 trial and 30.1% (95% CI, 13.0 to 47.1) in the SELECT-PsA 2 trial. In the SELECT-PsA 1 trial, this end point was included in the hierarchical statistical analysis; however, it was ranked after the hierarchical analysis failed and stopped so no appropriate statistical comparisons can be made. In the SELECT-PsA 2 study, this end point was not part of the multiplicity-controlled analyses. Thus, results for this end point are considered exploratory in both trials.

Change in axial disease was assessed in patients with the presence of psoriatic spondylitis at baseline. The improvement in BASDAI score from baseline to week 24 numerically favoured the upadacitinib 15 mg treatment group compared with placebo in both studies and compared with adalimumab in the SELECT-PsA 1 study. In the SELECT-PsA 1 study, the difference in the LS mean change in scores from baseline between upadacitinib and adalimumab was −0.57 (95% CI, −1.09 to −0.05); between upadacitinib and placebo it was −1.42 (95% CI, −1.94 to −0.90). In the SELECT-PsA 2 study, the difference between upadacitinib and placebo was −1.85 (95% CI, −2.55 to −1.15). However, this outcome

assessment was not included in the hierarchical statistical analysis and should be considered inconclusive because of the potential for inflated type I error.

Radiographic Changes

Radiographic change was assessed only in the SELECT-PsA 1 study using the Sharp/van der Heijde score (SHS). At week 24, the differences in LS mean change from baseline for the SHS was statistically significant, favouring the upadacitinib 15 mg treatment group over placebo (−0.29; 95% CI, −0.44 to −0.14; P = 0.0004). According to the clinical expert consulted on this review, the numerically small changes seen are unlikely to be clinically meaningful to patients over a period of only 24 weeks and that it is difficult to extrapolate the significance of these changes over the lifetime of a patient with PsA. In particular, it is uncertain whether the radiographic changes seen in the SELECT-PsA 1 study correlate with a direct, meaningful improvement in a patient's physical function, quality of life, or permanent disability. However, the observations satisfy the regulatory requirement that upadacitinib can inhibit radiographic progression.

Harms Results

By week 24, the proportion of patients in the SELECT-PsA 1 study who experienced a treatment-emergent AE (TEAE) was higher in the upadacitinib 15 mg and adalimumab treatment groups compared with the placebo group. In the SELECT-PsA 2 study, the proportion of patients who experienced a TEAE was similar between the upadacitinib and placebo groups. Generally, the majority of AEs were mild or moderate in severity; the most frequently reported AE in both studies was upper respiratory tract infection. The frequencies of serious AEs (SAEs) and withdrawal due to AEs (WDAEs) were low across all treatment groups, and generally below 5%, with the exception of the upadacitinib 15 mg treatment group in the SELECT-PsA 2 study which had the highest proportion of patients experiencing a SAE (5.7%) or WDAE (7.1%) across both studies. None of the specific SAEs were reported by more than 2 patients. Two treatment-emergent deaths were reported by week 24, both in the placebo group. One non−treatment-emergent death (i.e., occurring more than 30 days after the last dose) was reported in the upadacitinib 15 mg group.

Critical Appraisal

- Key end points comparing upadacitinib to adalimumab were measured at week 12. According to the clinical expert consulted for this review, this may not have provided adequate time for adalimumab to show maximal benefit. The benefit of JAK inhibitors is generally seen sooner than TNF inhibitors; as such, end points measured at week 12 may be biased in favour of upadacitinib. Although results of both upadacitinib and adalimumab were consistent until 24 weeks, it is uncertain whether upadacitinib 15 mg is noninferior to adalimumab due to lack of statistical testing at week 24. Also, the non-inferiority and superiority comparisons between upadacitinib and adalimumab were conducted for the ACR20 efficacy outcome only; hence, it is unclear whether upadacitinib would be noninferior to adalimumab for other important outcome measures.

- Some end points measured in this trial may not be considered clinically meaningful to patients, despite showing statistically significant differences in the trials. For example, subjective measures such as fatigue or the small changes seen in the SHS may not reflect clinically meaningful improvement, especially when measured over such a short length of time relative to the long disease course. The clinical expert consulted for this review noted that it is difficult to extrapolate the significance of these changes over the lifetime of a patient with PsA. Also, several outcomes that were identified in the CADTH review protocol

and reported in the studies fell outside the statistical testing hierarchy and thus need to be interpreted with consideration of type I error. Furthermore, the results of the pre-specified subgroup analyses performed for the primary end point should be interpreted with caution due to the small sample sizes, lack of control for type I error, and because the trial was not powered to test specific hypotheses in subgroups. As with the end points which were not part of the statistical testing hierarchy, the results of these subgroup analyses should be interpreted with caution.

- The SELECT-PsA 1 study required patients have either 1 or more erosions on X-ray or high-sensitivity C-reactive protein greater than the upper limit of normal for inclusion into the study, which could impact the generalizability of this study's results. According to the clinical expert consulted for this review, a substantial proportion of patients seen in clinical practice generally do not have evident erosions or inflammatory markers elevated to this degree yet still require treatment with bDMARDs.

- Although long-term data were reported for up to week 56 for both studies, placebo-controlled data for upadacitinib exists only up to week 24.

- Upadacitinib was compared to active treatment (adalimumab) only in patients with no prior exposure to bDMARD treatment. It is unknown if the same relative benefit can be expected from patients who have failed prior treatment with bDMARDs.

Indirect Comparisons

Description of Studies

Other than the inclusion of upadacitinib in the SELECT-PsA 1 and SELECT-PsA 2 studies, there are no studies in which upadacitinib has been compared directly to other bDMARDs or tsDMARDs. Therefore, the sponsor conducted an indirect comparison that comprised a network meta-analysis (NMA) that compared the efficacy of upadacitinib to that of TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), IL-17 inhibitors (secukinumab, ixekizumab), IL-12/23 inhibitor (ustekinumab), IL-23 inhibitor (guselkumab), CTLA4-Ig (abatacept), JAK inhibitors (tofacitinib), and PDE4 inhibitor (apremilast). Results from the ITC are summarized subsequently only for relevant comparators identified in the CADTH systematic review. Efficacy was compared at 12 and 24 weeks, and the ITC reported results for bDMARD-naive and bDMARD-experienced patients separately.

Efficacy Results

Overall, in bDMARD-naive patients, the NMA suggests that upadacitinib 15 mg is more efficacious for ACR response at week 12 compared with some comparators, specifically an IL-17 inhibitor (secukinumab 15 mg), IL-12/23 inhibitor (ustekinumab 45 mg), and IL-23 inhibitor (guselkumab), but this advantage was only seen for the IL-12/23 inhibitor at 24 weeks. Upadacitinib was also shown to be more efficacious than etanercept at both weeks 12 and 24 for PASI response; however, this was not seen with other TNF inhibitors. On the other hand, the IL-17 inhibitors (secukinumab 300 mg, ixekizumab) and IL-23 inhibitor (guselkumab) appear to be more efficacious than upadacitinib for PASI at week 12, although only the IL-23 inhibitor was favoured over upadacitinib at week 24. For PsARC, upadacitinib was more efficacious than tofacitinib but only at week 12; this was not seen at week 24. For HAQ-DI measured in PsARC responders at week 12, etanercept was shown to be more efficacious than upadacitinib; this benefit was not seen with other TNF inhibitors. At week 24, adalimumab appeared to be more efficacious than upadacitinib. Of note, the number of comparators included in some analyses (i.e., HAQ-DI at 24 weeks) was very limited. For

other analyses conducted, no difference was seen between upadacitinib and the relevant comparators. Thus, no consistent benefit of upadacitinib over bDMARDs or tsDMARDs was demonstrated across all measured end points at weeks 12 and 24.

In bDMARD-experienced patients, upadacitinib 15 mg was favoured only when compared to tofacitinib (JAK inhibitor) in PASI response at week 12; this comparison was not performed at week 24. No difference in treatment effect was demonstrated in all other comparisons between upadacitinib and included IL-inhibitors. Not all IL-inhibitors were included in every analysis, in particular, the IL-23 inhibitor was absent from many comparisons. Furthermore, TNF inhibitors were not included in any of the NMA analyses since there were insufficient eligible data in the bDMARD-experienced patient population, thus no conclusions can be drawn on the comparative efficacy of upadacitinib in these patients. Also, JAK inhibitors were not included in any of the week 24 analyses; therefore, the long-term comparative efficacy of upadacitinib compared with tofacitinib is unknown.

Harms Results

The sponsor's submitted ITC did not report safety outcomes.

Critical Appraisal

There are several limitations that increase the uncertainty in the results of the ITC discussed in this review. The included studies were highly heterogeneous in terms of inclusion criteria and patient characteristics. Significant differences were noted in potential effect modifiers, such as duration of disease, use of prior DMARDs, and disease severity. These factors are heightened due to the variation in inclusion and exclusion criteria across included studies. Yet, no sensitivity analysis or subgroup analysis was conducted to assess the impact of these potential effect modifiers on the comparison of upadacitinib and other biologics. The ITC also did not include any analyses of other clinically meaningful outcomes such as PsA symptoms (e.g., pain and fatigue), HRQoL, or safety.

Overall, there is uncertainty due to the inherent heterogeneity across trials in the networks. The robustness of the comparative efficacy was further compromised by the lack of precision in the findings, hence results from the sponsor-submitted ITC must be interpreted with caution.

Other Relevant Evidence

Description of Studies

Each of the 2 SELECT studies included 2 study periods. At the time of this review, data up to the end of period 1 (week 56) were available. Period 1 for the SELECT-PsA 1 study included 24 weeks of randomized, double-blind, placebo- and active comparator-controlled treatment followed by an additional 32 weeks of blinded active comparator-controlled treatment. Period 1 for the SELECT-PsA 2 study included 24 weeks of randomized, double-blind, placebo-controlled treatment followed by an additional 32 weeks of upadacitinib treatment. In both studies, all patients assigned to placebo were switched to pre-assigned upadacitinib 15 mg or 30 mg daily in a 1:1 ratio at week 24. Data reported at week 56 used the "as observed" dataset, and no adjustments for multiple testing were employed.

Efficacy Results

In both studies, results from the end of period 1 (week 56 data) suggest that the improvements in clinical and patient-reported outcomes observed at week 24 in patients who received upadacitinib 15 mg once daily starting at day 1 were maintained throughout the 56-week blinded treatment period. Patients who switched from placebo to upadacitinib 15 mg once daily at week 24 also showed improvements in clinical and patient-reported outcomes at week 56; the trajectory for the achievement of response or improvement in end points after starting upadacitinib was similar to those observed in patients who started upadacitinib on day 1 of both studies. Numerically greater improvement with upadacitinib compared with adalimumab was also demonstrated for several end points in the SELECT-PsA 1 study. For example, the difference in ACR20 response rate between the upadacitinib 15 mg treatment group (including those who switched to upadacitinib 15 mg from placebo) and adalimumab was 6.3% (95% CI, 0.3 to 12.2), and the difference in the proportion of patients achieving MDA was 7.6% (95% CI, 0.4 to 14.8).

Harms Results

The safety profile of oral upadacitinib 15 mg once daily over 56 weeks was consistent with that observed during the 24-week double-blind period in both the SELECT-PsA 1 and SELECT-PsA 2 studies, with no unexpected safety signals reported. Harms for the week 56 analysis were presented as exposure-adjusted event rates and were pooled, such that the data reported for upadacitinib exposure combined the upadacitinib 15 mg group and the placebo switched to upadacitinib 15 mg group. In the SELECT-PsA 1 study, 1 or more AEs were reported at an exposure-adjusted incidence of 265.9 events per 100 patient-years (PY) in the adalimumab group and 281.1 events per 100 PY in the upadacitinib group. In the SELECT-PsA 2 study, 1 or more AEs were reported at a rate of 260.6 events per 100 PY (pooled upadacitinib group). With longer exposure to treatment, a greater proportion of patients treated with upadacitinib compared with adalimumab experienced infectious AEs, including the following (presented as events per 100 PY): urinary tract infections (3.6 for adalimumab and 6.7 for upadacitinib in SELECT-PsA 1; 9.8 for upadacitinib in SELECT-PsA 2), bronchitis (2.9 for adalimumab and 5.7 for upadacitinib in SELECT-PsA 1; 8.8 for upadacitinib in SELECT-PsA 2), hypertension (2.7 for adalimumab and 5.6 for upadacitinib in SELECT-PsA 1; 5.7 for upadacitinib in SELECT-PsA 2), and influenza (0.8 for adalimumab and 3.2 for upadacitinib in SELECT-PsA 1; 5.2 for upadacitinib in SELECT-PsA 2). Herpes zoster was also reported in a higher proportion of patients treated with upadacitinib across both studies (3.9 per 100 PY and 3.8 per 100 PY in SELECT-PsA 1 and SELECT-PsA 2, respectively) compared to those treated with adalimumab (0.5 per 100 PY). Other notable AEs that showed an imbalance in the groups included CPK elevation and hepatic disorder, which were reported at a higher incidence by both upadacitinib and adalimumab treatment groups in the SELECT-PsA 1 study compared with the SELECT-PsA 2 study. Elevated CPK levels were reported at an incidence (per 100 PY) of 7.3 for adalimumab and 11.9 for upadacitinib in the SELECT-PsA 1 study and 5.2 for upadacitinib in the SELECT-PsA 2 study. Hepatic disorder was reported in a higher proportion of patients treated with adalimumab (per 100 PY: 24.9 for adalimumab and 19.1 for upadacitinib in SELECT-PsA 1; 4.8 for upadacitinib in SELECT-PsA 2), and may be confounded overall by the higher usage of concomitant methotrexate treatment in SELECT-PsA 1 patients. Withdrawal of treatment due to AEs was reported at an incidence of 7.4 per 100 PY for adalimumab in SELECT-PsA 1, and 4.6 per 100 PY and 10.0 per 100 PY for upadacitinib in SELECT-PsA 1 and SELECT-PsA 2, respectively. In total, 5 deaths occurred in the relevant treatment groups by the end of period 1, inclusive of those counted within week 24 data. These include both treatment-emergent (occurring within 30 days of last dose for

upadacitinib or 70 days for adalimumab) and non-treatment-emergent deaths. One treatment-emergent death occurred in the adalimumab group and 2 non−treatment-emergent deaths occurred in the upadacitinib 15 mg treatment group. The remaining 2 deaths occurred in the placebo groups.

Critical Appraisal

The interpretation of the long-term efficacy and safety outcomes at week 56 is limited by a lack of placebo control in both the SELECT-PsA 1 and SELECT-PsA 2 studies, as well as lack of a comparator in the SELECT-PsA 2 study. Also, background therapies were allowed to be modified. As a result, it is difficult to disentangle the drug effect from the changes in the background therapies on the reported outcomes. Furthermore, given that all patients were aware that they were receiving an active treatment (upadacitinib or adalimumab), results for patient-reported outcomes may be subject to bias. No adjustment was made for multiplicity to evaluate long-term data; thus, given the large number of analyses performed, there is a risk of inflated type I error. As such, the 56-week data should be interpreted with caution.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults (age 18 years or older) with active PsA who have had an inadequate response to previous DMARDs or for whom DMARDs are not tolerated or contraindicated.
Treatment	A drug sequence initiated with upadacitinib as monotherapy or in combination with a non-bDMARD (not stratified)
Submitted price	$48.68 per upadacitinib 15 mg tablet
Treatment cost	The sponsor assumed 58% of patients would receive concomitant methotrexate as part of treatment (7.5 mg weekly); therefore, the combined total annual drug acquisition costs of upadacitinib with or without methotrexate was $17,867

Comparators	Drug sequences initiated with:
	• bDMARD-naive population:
	  ○ anti-TNFs (i.e., etanercept, infliximab, certolizumab pegol, adalimumab, golimumab)
	  ○ IL-17s (i.e., secukinumab, ixekizumab)
	  ○ IL-12/23 (i.e., ustekinumab)
	  ○ PDE4 (i.e., apremilast)
	• bDMARD-experienced population:
	  ○ IL-17 (i.e., secukinumab, ixekizumab)
	  ○ IL-12/23 (i.e., ustekinumab)

Perspective	Canadian publicly funded health care payer

Component	Description
Outcome	QALYs
Time horizon	Lifetime (48.5 years)
Key data source	• Unpublished sponsor-commissioned NMAs to inform efficacy (i.e., ACR 20/50/70, PsARC, HAQ-DI score, and PASI 50/75/90) • SELECT-PsA 1 and SELECT-PsA 2 studies to inform health state utilities (i.e., EQ-5D) and patient baseline characteristics
Submitted results	bDMARD-naive population: • The efficiency frontier comprised apremilast sequence and upadacitinib sequence; all other treatments were dominated or extendedly dominated • ICER = $37,233 per QALY ($16,483 incremental costs; 0.443 incremental QALYs) vs. the apremilast sequence bDMARD-experienced population: • The efficiency frontier comprised the upadacitinib sequence only; all other treatments were dominated
Key limitations	• The treatments modelled were not fully reflective of Canadian clinical practice. The inclusion of apremilast for bDMARD-naive patients was not appropriate because an agreement on price has not been reached with the pCPA, and the generalizability of the results may be limited because treatments were not stratified as monotherapy or combination therapy. • The modelled clinical effectiveness of upadacitinib is uncertain. The sponsor-commissioned NMAs had limitations, which lead to the CADTH clinical review noting that the results should be viewed with caution; however, based on all the evidence, the clinical review found that upadacitinib does not show any difference in efficacy in terms of PsARC, PASI, HAQ-DI change, and ACR when compared to bDMARDs and tsDMARDs. Additionally, the long-term efficacy of upadacitinib is highly uncertain given the lack of available data. • The sponsor modelled a change in PsARC within the model. Feedback from the clinical expert consulted by CADTH noted that, although it is required by some jurisdictions, PsARC is not commonly used as a measure of response in practice. • Inclusions of subsequent treatments biased the results in terms of costs and effects in favour of upadacitinib, although still not being reflective of Canadian clinical practice.
CADTH reanalysis results	• CADTH undertook reanalyses that excluded apremilast and subsequent treatments and included wastage for infliximab. CADTH also undertook a scenario analysis assuming all patients receiving adalimumab received the biosimilar at the available list price. CADTH could not address limitations with the clinical data. • The results of the CADTH reanalyses indicated that upadacitinib was dominated by (i.e., more costly and less effective than) etanercept in the bDMARD-naive population and by secukinumab in the bDMARD-experienced population. • Based on the CADTH base case, a price reduction of 5% to 27% is required for upadacitinib to move onto the cost-effectiveness frontier.

ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire – Disability Index; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; QALY = quality-adjusted life-year; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

• Market growth for use of bDMARDs in patients with PsA is uncertain and may have been overestimated.

- There is uncertainty in the market uptake assumptions for upadacitinib, including how it would displace the market shares of comparator treatments and how functional and generalizable the budget impact is for the Canadian setting.
- The projected cost of adalimumab is overestimated given the recent availability of new biosimilar products.
- Patient copayments were included in the base case; however, these were removed in reanalyses.

The CADTH reanalyses included removing patient copayments; adding additional administrative costs, which reduced the cost savings associated with upadacitinib. When the price of biosimilar adalimumab was assumed for all adalimumab patients, upadacitinib was no longer cost saving. A larger incremental cost occurred when assuming 100% biosimilar costs for infliximab and etanercept as well as adalimumab. Based on the reanalyses, the 3-year budget impact estimates ranged from an incremental cost of approximately $3.1 million to a cost saving of approximately $2.5 million.

Because CADTH was unable to easily revise the treatments displaced by upadacitinib, and because the actual prices paid by drug programs are unknown, the budget impact of reimbursing upadacitinib for this indication is associated with some uncertainty.

Members of the Canadian Drug Expert Committee

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

Meeting date: June 16, 2021

Regrets: One CDEC member did not attend

Conflicts of interest: None