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Reimbursement Recommendation

Tofacitinib

Reimbursement request: For the treatment of active polyarticular juvenile idiopathic arthritis (pJIA; rheumatoid factor positive [RF-positive] or rheumatoid factor negative [RF-negative] polyarthritis, extended oligoarthritis, and systemic JIA [sJIA] without active systemic manifestations), juvenile psoriatic arthritis (JPsA), and enthesitis-related arthritis (ERA) in children who have responded inadequately or are intolerant to tumour necrosis factor (TNF) inhibitors or when use of those therapies is inadvisable.

Requester: Public drug programs

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Tofacitinib?

The Formulary Management Expert Committee (FMEC) recommends that tofacitinib be reimbursed for the treatment of patients with juvenile idiopathic arthritis (JIA) provided certain conditions are met.

What Are the Conditions for Reimbursement?

Tofacitinib may be initiated for pediatric patients (between the age of 2 and below 18 years) for the treatment of JIA if all the following conditions are met. The patient must have a confirmed diagnosis of JIA, which includes the following subtypes: polyarticular course juvenile idiopathic arthritis (rheumatoid factor [RF]–positive polyarthritis, RF-negative polyarthritis, extended oligoarthritis, and systemic JIA without active systemic features), psoriatic arthritis, and enthesitis-related arthritis. The patient must also meet at least 1 of the following conditions related to methotrexate therapy: they have an inadequate response to methotrexate monotherapy at a maximum tolerated dose for at least 3 months; they have developed an intolerance to, or have a contraindication to, methotrexate therapy; or methotrexate is clinically inappropriate for the treatment of the patient's condition. In addition, the patient must have had an inadequate response to a tumour necrosis factor (TNF) inhibitor or TNF inhibitor use is clinically inappropriate for the patient. Tofacitinib must also represent good value to the drug plans.

Why Did CDA-AMC Make This Recommendation?

FMEC reviewed the Canada's Drug Agency (CDA-AMC) report, which included the PROPEL trial that compared tofacitinib to placebo in patients with polyarticular course JIA, 1 long-term extension study, 1 indirect treatment comparison, and a cost comparison of tofacitinib versus other treatments used in Canada. The PROPEL trial results suggest a difference between treatments, with tofacitinib showing a greater improvement in JIA flare rate by week 44, and a greater improvement of JIA American College of Rheumatology (ACR) 30% (ACR30), 50% (ACR50), and 70% (ACR70) responses at week 44 for patients with polyarticular course JIA relative to placebo.

FMEC also considered input received from Arthritis Consumer Experts; a joint submission from Arthritis Society Canada, Canadian Arthritis Patient Alliance, Canadian Spondyloarthritis Association, Cassie + Friends, and Psoriasis Canada; the Canadian Rheumatology Association; and public drug programs.

Summary

FMEC concluded that there was uncertainty in the clinical value demonstrated by tofacitinib and there is a significant clinical need arising from JIA despite available treatments. The reimbursement conditions were further developed based on distinct social and ethical considerations, economic considerations, and impacts on the health system.

Therapeutic Landscape

What Is JIA?

JIA is a chronic inflammatory disorder primarily involving the joints, with persistent joint swelling that can cause degradation of the articular cartilage and deformities of affected joints. JIA can be associated with concomitant uveitis (inflammation of the eyes) that can result in visual impairment, glaucoma, band keratopathy, and cataracts. Patients living with JIA experience physical challenges that negatively affect their mental health and their ability to participate in school, work, and activities of daily living and recreation. In fiscal year 2022–2023, it was estimated that 6,545 children aged from birth to 15 years were living with JIA in Canada and 865 children in this age group were newly diagnosed with JIA.

What Are the Current Treatment Options?

To manage JIA, treatments such as conventional synthetic disease-modifying antirheumatic drugs (DMARDs) (e.g., methotrexate) and/or biologic DMARDs (e.g., TNF inhibitors, abatacept, and tocilizumab) are necessary. Targeted synthetic DMARDs (e.g., Janus kinase [JAK] inhibitors: tofacitinib) are emerging therapies, especially for individuals with JIA whose disease has lacked a response or had an inadequate response to other therapies. Nonsteroidal anti-inflammatory drugs (NSAIDs) are mainly used to treat axial disease associated with psoriatic arthritis (with spinal involvement and common symptoms such as back pain) and as bridging therapy while awaiting the onset of treatment effects with a DMARD. Systemic glucocorticoids are primarily used in patients with severe systemic inflammation or severe debilitating polyarticular disease without fair symptomatic relief or control with NSAIDs.

What Is the Treatment Under Review?

Tofacitinib is a targeted synthetic DMARD and a potent selective inhibitor of the JAK family of kinases, particularly JAK1 and JAK3. Tofacitinib treats inflammation in autoimmune disease, including inflammatory arthritis such as JIA. The current review of tofacitinib encompasses both the Health Canada–approved indication for the treatment of children with active polyarticular JIA (RF-positive or RF-negative polyarthritis, extended oligoarthritis, and systemic JIA without systemic manifestations), psoriatic arthritis, and as an off-label indication for the treatment of children with enthesitis-related arthritis.

Why Did We Conduct This Review?

Following clinicians' interest in accessing tofacitinib for the treatment of JIA, the public drug programs requested a nonsponsored review be conducted to inform a reimbursement recommendation for tofacitinib for the treatment of active polyarticular JIA (RF-positive or RF-negative polyarthritis, extended oligoarthritis, and systemic arthritis without systemic manifestations), juvenile psoriatic arthritis, and enthesitis-related arthritis in children who have responded inadequately or are intolerant to TNF inhibitors or when use of those therapies is inadvisable. Tofacitinib offers a novel mechanism of action and is available as an oral tablet. Tofacitinib could potentially fulfill an unmet need in the pediatric population.

Data protection for tofacitinib expired on October 17, 2022, and several generics are already approved and available in Canada. Because tofacitinib is a drug that is later in its life cycle, it is eligible for a nonsponsored reimbursement review as per the Procedures for Reimbursement Reviews.

Input From Interested Parties

- Two patient groups, **ACE** and a joint submission (**Arthritis Society Canada, Canadian Arthritis Patient Alliance, Canadian Spondyloarthritis Association, Cassie + Friends, and Psoriasis Canada**) advocated for patients living with JIA and their caregivers to have access to additional treatment options, particularly those with alternative forms of administration, such as an oral medication that could potentially address the anxiety and pain related to injection treatments. The goals of treatment identified by the patient groups include reduced joint swelling and pain, improved health-related quality of life (HRQoL), including school participation, engagement in social activities, and reduced parent or caregiver burden. Patients and their parents or caregivers also identified challenges accessing accommodations at school or work and with accessing high-quality care (e.g., information on available pharmacological and nonpharmacological treatments, access to insurance coverage and extended health benefits including support for administrative processes, and improved access to rheumatologists).
- One clinician group, the **Canadian Rheumatology Association**, indicated that the goal of treatment for patients with JIA is to achieve inactive disease with full, pain-free function by controlling joint inflammation and pain thereby improving daily functional ability and overall well-being.
- **Public drug plans** inquired about the evidence for tofacitinib to inform a recommendation about whether it should be reimbursed for children with active polyarticular JIA, psoriatic arthritis, or enthesitis-related arthritis who have responded inadequately or are intolerant to TNF inhibitors or when use of those therapies is inadvisable. The public drug plans outlined implementation questions related to treatment eligibility, prescribing, and care provisions.

► **Refer to the main report and the supplemental material document for this** review.

Person With Lived Experience

A graduate student from Ontario shared her journey with JIA, spotlighting her experience living with JIA as an adolescent. Issues in multiple joints made walking, sleeping, and activities of daily living difficult. A diagnosis was a relief when it finally came in her mid-teens. She worried about potential treatment side effects, such as hair loss. She trialled various drugs, including several TNF inhibitors, before starting tofacitinib, which she received through a patient assistance program. She found tofacitinib effective, tolerable, and easy to take. A significant benefit was the freedom a once-daily oral medication offered compared to injections and infusions. She received help from her mother to manage her condition and from some accommodations at school, but she noted a general lack of support for people with JIA. She emphasized the importance of the patient voice in matters of access and care.

Disclaimer: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person, or caregiver might go through when facing this condition or treatment, helping to inform the committee's deliberations. These narratives complement other forms of evidence and input and should be considered as part of a broader understanding of the condition and treatment under review. Where gender or gendered pronouns are used in these narratives, they are included with the permission of the individual.

Summary of Deliberation

FMEC deliberated on all domains of value of the deliberative framework before developing their recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, please refer to the Expert Committee Deliberation at Canada's Drug Agency document.

FMEC considered the following key discussion points, organized by the 5 domains of value.

Clinical Value

FMEC concluded that it is uncertain whether tofacitinib demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.

- Through reflection on the input from patient groups or insights shared by the person with lived experience, FMEC members noted the following important patient values or perspectives: core outcomes for JIA (e.g., pain, joint inflammatory signs, activity limitation or physical function, patient well-being, and adverse events) that are endorsed by Outcome Measures in Rheumatology (OMERACT) reflect outcome domains important to children and their families and are preferred over end points commonly used in clinical trials (e.g., ACR70 or ACR 90% response [ACR90]). Patient-reported outcomes beyond generic HRQoL measures, such as school participation, engagement in social activities, and parent or caregiver burden, are also identified as important by patients and their caregivers.

FMEC members highlighted the following discussion points:

- Based on the PROPEL trial, patients in the tofacitinib group experienced fewer disease flares than those in the placebo group (29% versus 53%; difference in JIA flare rate = −24%; 95% CI, −39% to 8%; P = 0.0031). Time to JIA flare demonstrated a 54% reduction in flare risk (hazard ratio [HR] = 0.46; 95% CI, 0.27 to 0.79; P = 0.0037). Response rates were higher in the tofacitinib group than the placebo group for JIA ACR30 (71% versus 47%), JIA ACR50 (67% versus 47%), and JIA ACR70 (54% versus 37%).
- FMEC agreed that the primary outcome of occurrence of a JIA flare at week 44 aligns with the overall treatment goal of achieving disease control and remission. However, FMEC noted limitations in the use of assessment tools designed for clinical trials (e.g., ACR response), which are neither routinely performed in real-world clinical practice nor aligned with outcomes important to patients.
- FMEC indicated there were several limitations in the evidence that contributed to the uncertainty in the efficacy of tofacitinib. Based on the randomized withdrawal design of the PROPEL trial, patients who both tolerated and responded to treatment were selected for randomization, potentially resulting in an enriched population of individuals who were more likely to benefit from or tolerate treatment. Furthermore, the use of placebo in addition to standard of care did not align with the availability of other treatments currently used in clinical practice in Canada. Although the network meta-analysis included relevant treatments for JIA, some drugs do not have pediatric indications in Canada (e.g., secukinumab), which limits the alignment of comparators to clinical practice and the interpretation of findings.
- FMEC noted approximately 30% of patients in the PROPEL trial had prior biologic DMARD use, so the enrolled population comprised a mixed patient population of children with and without prior treatment with a TNF inhibitor. It was unknown why patients previously treated with a TNF inhibitor did not continue treatment with TNF inhibitors. No subgroup analysis was available for patients who had previously been exposed to TNF inhibitors.
- Evidence from the PROPEL trial reported mixed results for outcomes assessing physical function, pain, and HRQoL. FMEC discussed that if disease control is achieved with tofacitinib after failure with other treatments, then a clinical improvement in physical function can be expected, resulting in other positive impacts (e.g., emotional, behavioural, and intellectual development).
- FMEC noted that, based on evidence from the PROPEL trial, the risk of infection is likely similar for tofacitinib and for other classes of DMARDs. Additionally, findings from the long-term extension study did not result in new safety issues at up to 105 months of follow-up. Serious warnings and precautions in the product monograph for tofacitinib are based on safety data in adults (e.g., malignancies, major adverse cardiovascular events) and may not be applicable to the pediatric population.
- Although the committee concluded that it is uncertain whether tofacitinib demonstrates acceptable clinical value versus appropriate comparators based on the interval validity of the available evidence (due to risk of risk of bias and indirectness of the patient population), FMEC heard from the guest

specialists that they were certain of the external validity of the available evidence, specifically the generalizability of the beneficial clinical effects of tofacitinib in JIA in clinical practice.

Unmet Clinical Need

FMEC concluded there is a significant clinical need arising from JIA despite available treatments.

- Through reflection on the input from patient groups or insights shared by a person with lived experience, FMEC members noted the following important patient values or perspectives. Response to treatment and duration of response can vary significantly within and between individuals; therefore, patients and caregivers expressed a desire for more treatment options. Many children experience significant anxiety and fear related to injections and patients and their caregivers value the availability of oral treatments.

FMEC members highlighted the following discussion points:

- JIA is a relatively common condition affecting approximately 2 million children globally. There are large patient registries, established research groups, and multinational trials commonly conducted in this patient population.
- FMEC acknowledged that JIA is a chronic condition with substantial morbidity across all subtypes, negatively impacting multiple body systems, particularly the joints and eyes, and can lead to joint damage, chronic pain, and disability. Furthermore, JIA affects children's physical and mental development, which puts significant burdens on the child and their family.
- FMEC discussed the classes of medications available to manage JIA, including NSAIDs, glucocorticoids, conventional DMARDs, and biologic DMARDs, such as TNF inhibitors; there are risks of immunosuppression and infection across all the drug classes. Importantly, a large proportion of patients with JIA do not respond to currently available treatments or lose response to therapy over time.
- Despite the availability of biologic DMARDs, many patients continue to experience active JIA. FMEC agreed that, unlike biologics which act on single extracellular pathways, tofacitinib has a unique mechanism of action that targets multiple intracellular pathways, providing an important alternative treatment for patients who experience intolerance (e.g., adverse effects) or lack of response (e.g., treatment failure) to other biologic DMARDs.
- FMEC agreed that because tofacitinib is an oral therapy, it addresses an unmet clinical need for individuals who would benefit from therapies that are less invasive and easier to administer. In addition, 1 guest specialist highlighted that biologic DMARDs can only be kept outside of refrigeration for 2 weeks. This limits the ability of patients and their families to travel. The need for IV infusions also means that the lives of patients and their families are limited by their need to attend to routine infusions.

Distinct Social and Ethical Considerations

FMEC did not identify any important measures that should be implemented to ensure the use of tofacitinib addresses relevant social and ethical implications.

- Through reflection on the input from patient groups or insights shared by the person with lived experience, FMEC members noted the following important patient perspectives: other treatment options for JIA involve parenteral administration (subcutaneous or IV) and require travel to clinics for administration. These requirements are burdensome for patients and caregivers and may also affect developmental milestones if treatment interferes with school attendance. These parenteral treatments may also present significant barriers for individuals with needle aversion. Young patients have also expressed concerns regarding access to therapies and their ability to afford these medications in adulthood.

FMEC members highlighted the following discussion points:

- FMEC agreed that tofacitinib may address unmet clinical and nonclinical needs that exist despite available treatments. Because several biologic DMARDs require infusion administration in clinics, an oral therapy would reduce travel and associated burdens for individuals who reside in geographically remote or rural locations. There is also time spent onsite for the administration of treatment. Additionally, tofacitinib offers a mode of administration that may be more acceptable to patients with significant needle aversion, reduce potential trauma associated with parenteral medications, and improve compliance with therapy.
- FMEC agreed there were no concerns for any social or ethical issues regarding treatment with tofacitinib, acknowledging that parental consent is required, as with any medication under consideration. FMEC noted that access to this therapy and financial coverage during the transition to adulthood are ongoing concerns.
- FMEC highlighted that tofacitinib is classified as a hazardous medication as per the NIOSH List of Hazardous Drugs in Healthcare Settings, 2024 and additional precautions and handling requirements may be warranted. FMEC also noted that oral medications are associated with lower environmental impacts than biologic alternatives.
- FMEC noted that tofacitinib as an oral tablet is available in Canada specifically for patients weighing 40 kg or more; however, the oral solution formulation available in the PROPEL trial for children weighing less than 40 kg is not currently marketed or available in Canada. We also heard from 1 guest specialist that a compounded solution with a short expiry may be available in some settings.

Economic Considerations

- **FMEC concluded that there are economic considerations that are important to address when implementing tofacitinib.**
- **FMEC** members highlighted the following discussion points:

- At publicly available prices, the reimbursement of tofacitinib for JIA is expected to decrease overall drug acquisition costs compared with all relevant comparators. The difference between the cost of tofacitinib compared with the confidentially negotiated prices of its comparators is unknown.
- It is uncertain whether tofacitinib provides a clinically important advantage or disadvantage compared with any included comparator.
- Because tofacitinib is associated with lower drug acquisition costs at public list prices and its clinical benefits compared with other active comparators are uncertain, the reimbursement of tofacitinib may result in cost savings with uncertain benefits.
- Due to uncertainty in clinical benefits and drug acquisition costs, the cost of tofacitinib should not exceed the per-patient drug plan costs of the least costly therapy for this population of patients to reduce the uncertainty that tofacitinib provides good value.

Impacts on Health Systems

- **FMEC did not identify any impacts on health systems that are important to address when implementing tofacitinib**.
- **FMEC** members highlighted the following discussion points:
  - The implementation of orally administered tofacitinib could potentially displace other parenteral treatment options, thereby reducing patient visits at outpatient infusion clinics; there is also less frequent bloodwork monitoring compared with some biologic DMARDs (e.g., tocilizumab). The implementation of tofacitinib may reduce nursing or pharmacy resources for medication preparation and these resources can be reallocated for other patient care activities.
  - The implementation of tofacitinib would not require additional training, infrastructure, or use of technologies compared with alternatives.
  - FMEC noted that access to pediatric rheumatologists is limited in certain jurisdictions and that universal funding and access to suitable formulations of oral medications for all pediatric patients remains a challenge in Canada.

Full Recommendation

With a vote **of 7 to 0,** FMEC recommends that tofacitinib, for the treatment of pediatric patients with JIA, be reimbursed if the conditions presented in Table 1 are met.

Table 1: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Tofacitinib may be initiated for	In the PROPEL trial, treatment with	The PROPEL trial enrolled patients

Reimbursement condition	Reason	Implementation guidance
pediatric patients (between the age of 2 and below 18 years) for the treatment of JIA if all the following conditions are met: 1.1. The patient has a confirmed diagnosis of JIA, including any of the following subtypes: 1.1.1. polyarticular course juvenile idiopathic arthritis (RF-positive polyarthritis, RF-negative polyarthritis, extended oligoarthritis, and systemic JIA without active systemic features) 1.1.2. psoriatic arthritis 1.1.3. enthesitis-related arthritis. 1.2. At least 1 of the following conditions related to methotrexate therapy is met: 1.2.1. the patient has an inadequate response to methotrexate monotherapy at a maximum tolerated dose for at least 3 months 1.2.2. the patient has developed an intolerance to, or has a contraindication to, methotrexate therapy 1.2.3. methotrexate is clinically inappropriate for the treatment of the patient's condition. 1.3. The patient has an inadequate response to a TNF inhibitor or if TNF inhibitor use is clinically inappropriate.	tofacitinib signalled clinical benefit in patients aged 2 years to younger than 18 years with polyarticular course JIA (RF-positive and RF-negative polyarthritis, extended arthritis, and systemic JIA without systemic features), psoriatic arthritis, and enthesitis-related arthritis. The PROPEL trial included a mixed population of participants with and without prior TNF inhibitor experience. The majority of the enrolled population had not previously been treated with a TNF inhibitor. The reason for TNF inhibitor discontinuation in the group with TNF inhibitor experience was not reported.	who met the International League of Associations for Rheumatology classification criteria.[a] However, based on discussion with the guest specialists, the treatment landscape is evolving, and these classifications (e.g., those based on number of joint counts with active disease) may not align with current clinical practice and could inadvertently restrict treatment with tofacitinib in patients for whom it may be clinically appropriate. For implementation, jurisdictions may consider using the existing criteria for JIA. Based on consultation with guest specialists, initiating treatment with methotrexate in patients with psoriatic arthritis or enthesitis-related arthritis may not be clinically appropriate. For example, patients with axial disease or with spinal involvement may receive NSAIDs as first-line treatment. The guest specialists also noted that conventional DMARDs (e.g., methotrexate) have not consistently shown benefit in these patients. In the PROPEL trial, patients with polyarticular course JIA had to have an inadequate response to 1 or more DMARDs (methotrexate or biological DMARDs). For patients with psoriatic arthritis or enthesitis-related arthritis, they had to have an inadequate response to NSAIDs.
Maintenance and renewal		
2. Tofacitinib should be continued if there is objective evidence of improvement after 6 months.	Consistent with clinical practice, patients may continue therapy based on routine assessment of responses by a specialist.	Jurisdictions may implement maintenance and renewal criteria to align with their existing guidelines or policies.

Reimbursement condition	Reason	Implementation guidance
Prescribing		
3. Prescribing should be limited to clinicians with expertise in the diagnosis and management of JIA.	This will ensure that treatment is prescribed for patients for whom it is clinically appropriate and that adverse events are optimally managed.	—
Pricing		
4. Tofacitinib must represent good value to the drug plans.	Tofacitinib is associated with lower drug acquisition costs at publicly available prices vs. all comparators. Based on the available network meta-analysis, it is uncertain whether tofacitinib provides a clinically important advantage or disadvantage compared with any included comparator. Ensuring that the cost of tofacitinib does not exceed the per-patient drug plan cost of the least costly therapy for this population would reduce the uncertainty that tofacitinib would provide good value to drug plans.	—

DMARD = disease-modifying antirheumatic drug; JIA = juvenile idiopathic arthritis; NSAID = nonsteroidal anti-inflammatory drug; RF = rheumatoid factor; TNF = tumour necrosis factor.

[a]Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-392.

Feedback on Draft Recommendation

CDA-AMC received feedback from the public drug programs that was largely editorial in nature. These have been addressed to improve the clarity of the recommendation report. CDA-AMC received no feedback from external partners.

All feedback received in response to the draft recommendation is available on the CDA-AMC project web page.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, and Dr. Dominika Wranik. Two guest specialists from the Prairies participated in this review.

Meeting date: September 18, 2025

Regrets: One expert committee member did not attend the meeting.

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the individuals who presented directly to FMEC and to the patient organizations representing and supporting the community of those living with JIA, including the Canadian Arthritis Patient Alliance, Laurie Proulx, and Naomi Abrahams.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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