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CADTH Reimbursement Recommendation

Guselkumab (Tremfya)

Indication: For the treatment of adult patients with active psoriatic arthritis. Guselkumab can be used alone or in combination with a conventional disease modifying antirheumatic drug (e.g., methotrexate).

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Tremfya?

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

Which Patients Are Eligible for Coverage?

Tremfya should only be reimbursed to treat adult patients with active PsA according to the reimbursement criteria used for other biologic disease-modifying antirheumatic drugs (DMARDs) that are currently reimbursed by public drug plans.

What Are the Conditions for Reimbursement?

Tremfya 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 DMARDs or targeted synthetic DMARDs. Tremfya should not be reimbursed when used together with other biologic or targeted synthetic DMARDs for active PsA.

Why Did CADTH Make This Recommendation?

- Evidence from 3 clinical trials demonstrated that Tremfya improves PsA symptoms compared to treatment with placebo.
- Tremfya may meet some of the needs that are important to patients, including reducing symptoms such as joint pain, clearing psoriasis, and improving health-related quality of life (HRQoL).
- Based on CADTH's assessment of the health economic evidence, Tremfya does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Tremfya compared with the least costly biologic or targeted synthetic DMARDs.
- Based on public list prices, Tremfya is estimated to cost the public drug plans approximately $4.7 million over the next 3 years if reimbursed in the same manner as currently available biologic and targeted synthetic DMARDs.

Additional Information

What Is PsA?

Arthritis is the swelling and tenderness of 1 or more joints. There are different types of arthritis, one of which is PsA. People with PsA have skin lesions associated with psoriasis, and often have inflamed joints, including the large joints of the arms and legs, the smaller joints in the fingers and toes, and joints in the spine. Pain and stiffness of the affected joints are the most common symptoms, and many patients also experience fatigue. The prevalence of PsA is estimated to be 1 to 2 per 1,000 in the general population.

Unmet Needs in PsA

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

How Much Does Tremfya Cost?

Treatment with Tremfya is expected to cost approximately $21,418 per patient in the first 52 weeks, and $19,888 per patient per year thereafter.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that guselkumab be reimbursed for the treatment of adult patients with active PsA only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 3 double-blind, randomized controlled trials (RCTs) in adults with active PsA who had an inadequate response to standard therapies (the DISCOVER-2 study), who had an inadequate response to standard therapies with or without prior exposure to tumour necrosis factor (TNF) alpha inhibitors (the DISCOVER-1 study), or who had insufficient response or intolerance to a TNF-alpha inhibitors (the COSMOS study), guselkumab (100 mg subcutaneous [SC] at week 0, week 4, week 8, and every 8 weeks thereafter) 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 24 (the primary efficacy outcome). The difference between the guselkumab every 8 weeks group and the placebo treatment group was 29.8% (95% confidence interval [CI], 18.6% to 41.1%; P < 0.001) in the DISCOVER-1 trial, 31.2% (95% CI, 22.9% to 39.5%, P < 0.001) in the DISCOVER-2 trial, and 24.6% (95% CI, 14.1% to 35.2%, P < 0.001) for the COSMOS study. In addition, guselkumab 100 mg every 8 weeks was associated with statistically significant improvements when compared with placebo for other clinically relevant manifestations of PsA, including function and disability, as measured with the Health Assessment Questionnaire – Disability Index (HAQ-DI), 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 (IGA). 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 3 RCTs, guselkumab appears to address some of these important outcomes valued by patients.

At the sponsor-submitted price for guselkumab and publicly listed prices for all other comparators, guselkumab was more costly than most other biologic therapies reimbursed for the treatment of PsA. In the absence of direct comparative evidence against other biologic therapies, and due to the uncertainty associated with the indirect comparison, the total drug cost of guselkumab should not exceed the total drug cost of the least expensive biologic DMARD or targeted synthetic DMARD reimbursed for the treatment of PsA.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of guselkumab should be based on the criteria used by each of the public drug	There is no direct evidence that guselkumab is clinically superior or inferior to other biologic	—

Reimbursement condition	Reason	Implementation guidance
plans for reimbursement of biologic DMARDs for the treatment of adult patients with active PsA.	treatments currently reimbursed for the treatment of active PsA.	
Renewal		
2. Guselkumab should be renewed in a similar manner to other biologic DMARDs currently reimbursed for the treatment of adult patients with active PsA.	There is no evidence that guselkumab should be held to a different standard than other reimbursed options when considering renewal.	—
Discontinuation		
3. Guselkumab should be discontinued in a similar manner to other biologic DMARDs currently reimbursed for the treatment of adult patients with active PsA.	There is no evidence that guselkumab should be held to a different standard than other reimbursed options when considering discontinuation.	—
Prescribing		
4. Patients 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 guselkumab is prescribed to the most appropriate patients. In addition, there are several DMARD 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.	—
5. Guselkumab should not be reimbursed when used in combination with biologic DMARDs or targeted synthetic DMARDs for active PsA.	There is no evidence to determine the effects of guselkumab when used in combination with biologic DMARDs or targeted synthetic DMARDs in adult patients with active PsA.	—
Pricing		
6. Guselkumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly biologic DMARD or targeted synthetic DMARD reimbursed for the treatment of PsA.	There is insufficient evidence to justify a cost premium for guselkumab over the least expensive biologic DMARD or targeted synthetic DMARD reimbursed for the treatment of PsA.	—
Feasibility of adoption		
7. The feasibility of adoption of guselkumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

DMARD = disease-modifying antirheumatic drug; PsA = psoriatic arthritis.

Discussion Points

- CDEC noted that there was no direct evidence available to assess the safety and efficacy of guselkumab versus other biologic DMARDs or targeted synthetic DMARDs for the treatment of PsA. Indirect evidence was available from 1 published and 1 sponsor-submitted network meta-analysis (NMA) that examined the comparative short-term efficacy and safety of guselkumab versus other biologic DMARDs or targeted synthetic DMARDs. These NMAs were limited by the heterogeneity in the study designs and patient populations across the included studies and by the considerable uncertainty in the indirect estimates of effect. Given these limitations, there remains uncertainty in the comparative efficacy and safety of guselkumab.
- CDEC acknowledged that guselkumab has a different mechanism of action than other biologic drugs currently reimbursed for PsA and noted that guselkumab is an additional treatment option for adult patients with active PsA. However, with the lack of direct evidence with relevant comparators and the uncertainty in the results from the sponsor-submitted NMA, any clinical benefit derived from this novel mechanism remains unproven.
- PsA is a chronic condition that requires lifelong treatment. There is uncertainty regarding the long-term effectiveness and safety of guselkumab over other currently available biologic DMARDs or targeted synthetic DMARDs for the treatment of active PsA.
- CDEC discussed the place in therapy of guselkumab. According to the clinical expert, guselkumab may be used as first- or second-line biologic therapy. The clinical expert highlighted that guselkumab may be a preferred first-line treatment for patients with moderate psoriasis in addition to musculoskeletal disease.

Background

PsA is an inflammatory musculoskeletal disease with heterogenous presentation and disease course. While it is associated with psoriasis, PsA also presents with variable clinical features involving multiple domains, including peripheral arthritis, enthesitis (i.e., tenderness and swelling at the insertion of tendons and ligaments into bone), dactylitis (i.e., swelling of the whole digit), and axial disease (i.e., inflammation of the joints of the back). Pain and stiffness of the affected joints are the most predominant presenting symptoms, with fatigue also occurring in many patients. The prevalence of PsA varies, depending on the case definition and geography, and is estimated to be 1 to 2 per 1,000 in the general population. A population-based Canadian study estimated the age- and sex-standardized cumulative prevalence of PsA in Ontario to range from 0.09% in 2008 to 0.15% in 2015.

Several drug classes are used in the pharmacologic treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs), conventional DMARDs (i.e., methotrexate, sulfasalazine, and leflunomide), biologic DMARDs (i.e., TNF inhibitors, interleukin [IL]-23 inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors), and targeted synthetic DMARDs (e.g., apremilast, upadacitinib, or tofacitinib).

Guselkumab is a human immunoglobulin G1 lambda monoclonal antibody that binds to the IL-23 protein and inhibits its binding with cell surface IL-23 receptor. Guselkumab is approved for the treatment of adult patients with active PsA, alone or in combination with a conventional DMARD (e.g., methotrexate) and is available as a 100 mg/mL solution for

SC injection in either 1 mL prefilled syringes or patient-controlled injector devices. The recommended dose for PsA is 100 mg SC at week 0, week 4, and every 8 weeks thereafter.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of the 3 RCTs in adults with active PsA
- patients' perspectives gathered by patient groups: Arthritis Consumer Experts (ACE), the Canadian Association of Psoriasis Patients partnering with the Canadian Psoriasis Network, and the Canadian Arthritis Patient Alliance partnering with the Arthritis Society and CreakyJoints
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with PsA
- input from 1 clinician group, the Canadian Rheumatologist Psoriatic Arthritis Interest Group
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of indirect evidence from 2 NMAs
- a review of longer-term data from the uncontrolled extension phase of the 3 RCTs.

Stakeholder Perspectives

Patient Input

Three patient group inputs were submitted for this review from 6 different patient groups: ACE, the Canadian Association of Psoriasis Patients partnering with the Canadian Psoriasis Network, and the Canadian Arthritis Patient Alliance partnering with the Arthritis Society and CreakyJoints. To inform its submission, ACE used a patient survey, with 5 respondents, between December 2020 and January 2021, and 1 respondent from May 2022. The other 5 organizations collaborated in a joint survey that included a total of 71 respondents.

Respondents reported a range of symptoms that are difficult to manage, including joint stiffness (79%), fatigue (75%), changes in fingernails and toes (63%), hip pain (61%), back pain (51%), anxiety (47%), and stress (33%). With regards to the most significant impacts of PsA on their daily quality of life, respondents expressed that PsA interfered with work (54%), social connections (52%), self-esteem (50%), mental health (50%), intimacy (50%), family life (38%), and friendships (24%). Other impacts included embarrassment and self-consciousness from symptoms caused by PsA. As the disease reduces their mobility and ability to participate in activities and impacts their mental and social health, respondents indicated there are additional tasks or chores relegated to caregivers, such as cooking, cleaning, shopping, and supporting patients in getting to and from medical appointments.

Survey respondents indicated that they had experience with several treatment approaches, including NSAIDs, corticosteroids, conventional synthetic DMARDs such as methotrexate, and biologic DMARDs. Among them, 32% respondents considered biologic drugs as

very effective, followed by oral steroids (23%) and other DMARDs (21%). Respondents expressed their ongoing unmet needs of managing symptoms and tolerable side effects with current treatments.

Two respondents who had experience with guselkumab indicated that the drug was effective in terms of improving psoriasis and arthritis and slowing disease progression. Both respondents stated that they did not experience side effects.

Respondents expected new treatments to improve the following key outcomes: management of the symptoms (e.g., reducing pain and fatigue, increasing mobility); tolerable side effects; drug administration; improved ability to work and carry out tasks and daily activities; and quality of life.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

A substantial proportion of patients do not achieve a minimal response with their first therapy or lose their response over time. In addition, some treatments have more adverse effects than others. Thus, there is a need for medications with new mechanisms of action or a different safety profile to offer alternate treatment options for these patients with an inadequate response or intolerance to therapy. According to the clinical expert, guselkumab may be used as first- or second-line biologic therapy. It may be a preferred first-line treatment for patients with moderate psoriasis in addition to musculoskeletal disease. Guselkumab may be used in combination with methotrexate or leflunomide; however, there is no evidence to support its use in combination with other biologic drugs.

Response to therapy is based on a reduction in the number of inflamed joints, and improvement in the skin and patient-reported outcomes (i.e., assessment of pain, function, and fatigue). According to the clinical expert, a major improvement would be at least a 50% improvement, but may also include achievement of minimal disease activity and remission based on specific instruments. An initial response may be expected within 3 months of initiating therapy, with more significant improvement by 6 months after initiating therapy. The expert indicated that if a patient shows no change within 3 to 6 months, they would be considered nonresponders and may be switched to another medication. The expert stated that ideally, guselkumab would be prescribed by specialists who are familiar with the drug and its uses, or at least in consultation with a dermatologist or rheumatologist.

Clinician Group Input

CADTH received 1 clinician group input submission from the Canadian Rheumatologist Psoriatic Arthritis Interest Group, based on responses from 6 clinicians who are practising in academic and community settings. The group clinician input was largely in agreement with the input received from the clinician consulted by CADTH. No major contrary views from those provided by the clinical experts consulted by CADTH for this review were presented.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for guselkumab:

- relevant comparators

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- system and economic issues.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
DISCOVER-1 (a phase III, multicenter, double-blind RCT) did not compare the effect of guselkumab to another biologic comparator. However, the study included patients who had failed on standard therapy (i.e., apremilast [which is not covered in any Canadian jurisdiction for PsA], non-biologic DMARDs, NSAIDs, and TNF inhibitors.) DISCOVER-2 (a phase III, multicenter, double-blind RCT) assessed patients who failed on standard non-biologic therapies (apremilast [which is not covered in any Canadian jurisdiction for PsA], non-biologic DMARDs, and NSAIDs) COSMOS (an RCT) assessed patients who stopped ≤ 2 TNF inhibitors due to lack of efficacy or intolerance. There were no head-to-head phase III RCTs comparing guselkumab to other biologics such as TNF-alpha inhibitors (e.g., certolizumab, etanercept, infliximab, adalimumab, or golimumab) or interleukin inhibitors (e.g., IL17A [secukinumab or ixekizumab] or IL23 [ustekinumab]). The sponsor included patients who failed on TNF inhibitors but randomized patients to the trial drug or placebo. There is no evidence comparing noninferiority or superiority to current therapeutic options that are available on government-sponsored drug plans in Canadian jurisdictions.	Comment from the drug programs to inform CDEC deliberations.
Adalimumab, etanercept, and infliximab biosimilars are available for this condition and offer substantial discounts to jurisdictions. Ustekinumab's patent has expired and there are future biosimilars in phase III trials (e.g., Amgen's ABP 564) for the treatment of PsA. Head-to-head trials in this space are essential for public payers to consider listing on government-sponsored drug plans.	Comment from the drug programs to inform CDEC deliberations.
Considerations for Initiation of therapy	
In the DISCOVER-1 trial, only 30% of the study population had been treated with up to 2 anti-TNF therapies; however, the COSMOS trial did require all patients to fail 2 or fewer TNF inhibitors to be enrolled.	Comment from the drug programs to inform CDEC deliberations.
Patients in the DISCOVER 1 and 2 trials had to have an inadequate response to non-biologic DMARDs, apremilast, or NSAIDs. In addition, the DISCOVER-1 trial included patients who had received TNF inhibitors.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Initiation of therapy criteria would preferably be aligned with those of the medications currently listed among jurisdictions. This includes anti-TNF drugs and IL inhibitors. Alignment with initiation of therapy criteria of JAK inhibitors that have a reimburse recommendation from CADTH for PsA would be helpful to drug plans as well. Should the initiation criteria for PsA biologic drugs and JAK inhibitors be applied to guselkumab?	CDEC agreed with the clinical expert that the initiation criteria for guselkumab should be consistent with other biologic therapies.
Considerations for continuation or renewal of therapy	
Alignment of continuation or renewal of therapy criteria with other biologic drugs and JAK inhibitors in this therapeutic space would be desirable for the drug plans. Should the continuation or renewal criteria for PsA biologic therapies and JAK inhibitors be applied to guselkumab?	CDEC agreed with the clinical expert that the renewal criteria for guselkumab should be consistent with other biologic therapies.
Considerations for discontinuation of therapy	
Alignment of discontinuation of therapy criteria with other biologic therapies and JAK inhibitors would be preferred by the drug plans. Should the discontinuation criteria for PsA biologics and JAK inhibitors be applied to guselkumab?	CDEC agreed with the clinical expert that the discontinuation criteria for guselkumab should be consistent with other biologic therapies.
Considerations for prescribing of therapy	
In general, patients are restricted to 1 biologic drug at a time and permitted to switch from one biologic therapy to another following an adequate trial of the first biologic therapy if their disease is unresponsive to therapy, or due to serious adverse effects or contraindications. Patients are not permitted to switch back to a previously trialled biologic drug if their disease was deemed unresponsive to therapy. No restrictions are in place regarding the combination with conventional DMARDs. Should the same combination criteria for PsA biologic drugs and JAK inhibitors be applied to guselkumab?	CDEC agreed with the clinical expert that guselkumab may be used in combination with non-biologic systemic therapies, but not with other biologic treatments.
Alignment of prescribing therapy with other biologic drugs and JAK inhibitors would be preferred. Should similar prescribing criteria for PsA biologic drugs and JAK inhibitors be applied to guselkumab?	CDEC agreed with the clinical expert that the prescribing criteria for guselkumab should be consistent with other biologics.
System and economic issues	
Many jurisdictions have biosimilar initiatives and policies in place that involve removing originator biologic drugs and listing only the biosimilar molecule in this therapeutic space. When the pan-Canadian Budget Impact Assessment is adjusted to model all jurisdictions having a biosimilar initiative in place for adalimumab, etanercept, and infliximab, the addition of guselkumab increases the incremental cost from $2 million (3-year total with no biosimilar policy) to $10 million (3-year total with biosimilar policies in place). As a result, the addition of guselkumab to public drug plans results in a higher incremental cost, especially in jurisdictions with biosimilar initiatives in place. Negotiated values will require a price reduction comparable to the	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
confidential price of the least costly biosimilar to ensure the sustainability of drug plans.	
There are a significant number of biologic drugs that have been negotiated by the pCPA for the treatment of PsA and listed on government-sponsored drug plans. Is there evidence to support drug plans paying a price premium for guselkumab vs. the lowest cost biosimilar TNF inhibitor?	CDEC agreed with the clinical expert that guselkumab offers Canadian patients with PsA another treatment option and that there is no evidence for a price premium.

CDEC = Canadian Drug Expert Committee; DMARD = disease-modifying antirheumatic drug; IL = interleukin; JAK = Janus kinase; NSAID = nonsteroidal anti-inflammatory drug; pCPA = pan-Canadian Pharmaceutical Alliance; PsA = psoriatic arthritis; RCT = randomized controlled trial; TNF = tumour necrosis factor; vs. = versus.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Three double-blind placebo-controlled RCTs met the inclusion criteria for the systematic review. The pivotal trials (DISCOVER-1 and 2) included patients with active PsA who had an inadequate response to conventional DMARDs, apremilast, and/or NSAIDs. The DISCOVER-1 study (N = 381) enrolled a mixed population that included those with no prior biologic treatment experience, or up to 30% of patients who had previously received 1 or 2 prior TNF-alpha inhibitors. In the DISCOVER-2 trial, all patients enrolled were biologic-naive (N = 741). The COSMOS study enrolled patients with active PsA who were intolerant to or had an inadequate response to 1 or 2 TNF-alpha inhibitors (N = 285). The trials were mainly conducted in Europe, with some sites in Asia, the US, Australia, Israel, and Canada (the DISCOVER-1 trial only).

Patients were randomized to receive placebo or guselkumab 100 mg SC at week 0, week 4, and every 8 weeks thereafter for 24 weeks. The DISCOVER-1 and DISCOVER-2 trials also included a third treatment group (guselkumab 100 mg every 4 weeks), which was not consistent with the Health Canada–recommended dose and therefore was not included in this report. The total trial duration was 52 weeks (the DISCOVER-1 trial), 100 weeks (the DISCOVER-2 trial), and 48 weeks (the COSMOS trial), with patients receiving placebo switched to guselkumab starting at week 24. During the trials, patients could continue receiving methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, oral corticosteroids, or NSAIDS, if doses were stable and did not exceed the protocol-specified maximum dose. Early escape therapy consisting of conventional DMARDs, corticosteroids, or NSAIDS, or a switch to guselkumab (in the COSMOS trial) was available at week 16 for patients who had a less than 5% improvement in tender and swollen joint counts.

The primary outcome in all trials was the proportion of patients who achieved an American College of Rheumatology 20% improvement (ACR 20) at week 24. The ACR 20 was defined as a 20% or greater improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints), and a 20% or higher improvement from baseline in 3 of the 5 assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI, and C-reactive protein. Other

outcomes of interest included the change from baseline in HAQ-DI and SF-36 PCS, and the impact on plaque psoriasis (measured based on the IGA of Psoriasis or PASI response).

The mean age of patients enrolled ranged from 44.9 years (standard deviation [SD] = 11.9) to 49.1 years (SD = 12.3) across treatment groups in the 3 trials. The proportion of females ranged from 46% to 55%, and most patients were White (89% to 98%; not reported for COSMOS). The mean number of swollen joints was 9.0 (SD = 5.7) to 12.3 (SD = 6.9), and tender joints was 18.2 (SD = 10.7) to 21.6 (SD = 13.1). Approximately two-thirds of patients had psoriatic involvement that affected at least 3% of their body surface area. Two-thirds of patients reported enthesitis, while approximately 40% had dactylitis at baseline. The majority of patients were receiving methotrexate at baseline (54% to 63%) with a lower percentage receiving the other permitted conventional DMARDs (0% to 7%). In the DISCOVER trials, 14% to 20% of patients were receiving oral corticosteroids at baseline, compared with 4% to 5% of patients in the COSMOS study.

Efficacy Results

In the DISCOVER-1 study, 52.0% of patients in the guselkumab every 8 weeks group achieved ACR 20 response at 24 weeks, compared with 22.2% of patients in the placebo group. The absolute difference was 29.8% (95% CI, 18.6% to 41.1%; P < 0.001), favouring guselkumab every 8 weeks versus placebo. The proportion of patients who achieved at least a 50% improvement (ACR 50) was 29.9% versus 8.7% (absolute difference = 21.4%; 95% CI 12.1% to 30.7%) or 70% improvement (ACR 70) was 11.8% versus 5.6% (absolute difference = 6.4%; 95% CI, −0.3% to 13.1%) for the guselkumab every 8 weeks group versus the placebo group. However, ACR 50 and ACR 70 were not controlled for multiple testing and should be interpreted with consideration of the inflated risk of type I error rate.

Among patients who were biologic-naive (the DISCOVER-2 trial), 64.1% and 32.9% of patients achieved ACR 20 response at 24 weeks in the guselkumab every 8 week and placebo groups, respectively, with an absolute difference of 31.2% (95% CI, 22.9% to 39.5%; P < 0.001). The proportion of patients who achieved ACR 50 response was 31.5% versus 14.2% (absolute difference = 17.2%; 95% CI, 10.0% to 24.4%) and ACR 70 response was 18.5% versus 4.1% (absolute difference = 14.5%; 95% CI, 9.1% to 19.9%). ACR 50 and ACR 70 were not controlled for multiple testing (i.e., the type I error rate was not controlled).

For patients who were biologic-experienced and enrolled in the COSMOS study, 44.4% and 19.8% achieved ACR 20 response at week 24 in the guselkumab every 8 weeks and placebo groups, respectively. The absolute difference between groups favoured guselkumab every 8 weeks: 24.6% (95% CI, 14.1% to 35.2%; P < 0.001). The difference also favoured guselkumab every 8 weeks versus placebo for the proportion who achieved ACR 50 response (19.6% versus 5.2%; absolute difference = 14.3%; 95% CI, 7.2% to 21.4%; P < 0.001). ACR 70 response was achieved by 7.9% versus 1.0% of patients in the guselkumab every 8 weeks versus placebo groups with an absolute difference of 6.8% (95% CI, 2.6% to 11.1%). ACR 70 was not controlled for multiple testing.

In the DISCOVER trials, the odds ratios of ACR 20 response were generally consistent across subgroups based on prior TNF-alpha inhibitor use and use of non-biologic DMARDs, oral corticosteroids, or NSAIDs at baseline, although the trials may not have been powered to detect subgroup differences. The COSMOS study did not report data for any subgroups of interest to this review.

Disability was assessed based on the HAQ-DI, which is a patient-reported 20-question instrument that assesses the degree of difficulty a person had accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). The overall score is the average of 8 domains ranging from 0 (no disability) to 3 (completely disabled). The change from baseline to week 24 in the HAQ-DI favoured guselkumab every 8 weeks versus placebo in all trials. The least squares (LS) mean difference versus placebo reported was −0.25 (95% CI, −0.36 to −0.13; P < 0.001) in the DISCOVER-1 study, −0.24 (95% CI, −0.32 to −0.15; P < 0.001) in the DISCOVER-2 study, and −0.17 (95% CI, −0.28 to −0.06; P = 0.003) in the COSMOS study. Across the trials, the between-group and within-group differences did not exceed the 0.35 minimal important difference (MID) cited by the sponsor, with the exception of the change from baseline within the guselkumab every 8 weeks group in the DISCOVER-2 study.

The change from baseline to week 24 in the SF-36 PCS favoured guselkumab every 8 weeks versus placebo in all 3 studies. The LS mean difference was 4.1 (95% CI, 2.4 to 5.9; P < 0.001) in the DISCOVER-1 trial, 4.0 (95% CI, 2.7 to 5.2; P = 0.011) in the DISCOVER-2 trial, and 3.9 (95% CI, 2.5 to 5.4; P < 0.001) in the COSMOS study. The clinical study report defined at least a 5-point increase as clinically meaningful, but an MID of 3.74 points has also been reported in the literature. No statistically significant differences were detected between guselkumab every 8 weeks and placebo in the change from baseline to week 24 in the SF-36 Mental Component Summary.

In all trials, psoriasis skin disease outcome measures were analyzed in the subgroup of patients who had psoriasis affecting 3% or more of their body surface area and an IGA score of 2 or higher at baseline (55% to 74% of patients per treatment group). Psoriasis severity was assessed using composite physician-reported assessments: IGA and PASI response. For the IGA, the severity of the patient's psoriasis is scored as cleared (0), minimal (1), mild (2), moderate (3), or severe (4). IGA response was defined as a score of 0 or 1, and at least a 2-point decrease from baseline. The PASI rates the extent and severity of psoriasis and is scored from 0 to 72 points, with a PASI score of higher than 10 considered to be severe disease. Patients with a 90% improvement or 100% improvement in their PASI score would meet PASI 90 or PASI 100 response criteria.

The proportion of patients who achieved an IGA response at week 24 was higher in the guselkumab every 8 weeks groups than the placebo group in the DISCOVER-1 study (57.3% versus 15.4%; absolute difference = 42.0%; 95% CI, 28.9% to 55.1%; P < 0.001]) and the DISCOVER-2 study (70.5% versus 19.1%; absolute difference = 50.9%; 95% CI, 42.2% to 59.7%; P < 0.001]). In the COSMOS study, 48.1% versus 9.4% of patients in the guselkumab every 8 week versus placebo group achieved an IGA response with an absolute difference of 38.8% (95% CI, 27.3% to 50.4%), but the P value has not been adjusted to control for multiple testing and thus should be interpreted with caution because of the potential for inflated type I error rate. PASI 100 response at week 24 was a secondary outcome in the COSMOS study. In the guselkumab group, 30.8% of patients achieved a PASI 100 response compared with 3.8% of patients in the placebo group (absolute difference = 27.4%; 95% CI, 17.9% to 36.8%; P < 0.001). In the DISCOVER trials, the proportion of patients who achieved a PASI 100 response was nominally higher for the guselkumab groups versus the placebo groups; however, these outcomes were not controlled for multiple testing and should be interpreted with consideration of the inflated risk of type I error rate.

For patients with enthesitis or dactylitis at baseline, the results of the DISCOVER-2 and COSMOS studies suggest an improvement in enthesitis or dactylitis end points with

guselkumab every 8 weeks relative to placebo, but no statistically significant difference was detected between groups in the DISCOVER-1 study. Based on the pre-planned pooled analysis of data from the DISCOVER trials, 49.6% and 29.4% of patients in the guselkumab every 8 week and placebo groups had resolution of enthesitis at week 24 with a between-group difference of 20.1% (95% CI, 11.8% to 28.5%; P = 0.03). The proportion of patients whose dactylitis resolved at week 24 was 59.4% versus 42.2% in the guselkumab every 8 weeks group versus the placebo group (between-group difference = 18.0%; 95% CI, 7.4% to 28.6%; P = 0.03). None of the trials detected a statistically significant difference between guselkumab every 8 weeks and placebo in the proportion of patients who reported a clinically important improvement in axial disease based on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). It is noteworthy that these outcomes were tested in subgroups of patients that may not be balanced between treatment groups with respect to baseline demographic and disease characteristics due to the lack of stratification at randomization.

Symptoms of fatigue were assessment based on the Functional Assessment of Chronic Illness Therapy – Fatigue questionnaire (FACIT-Fatigue). The score ranges from 0 to 52, with lower scores reflecting more severe fatigue. Estimates of the MID range from 3.1 points to 4 points. The DISCOVER-1 study reported an LS mean difference of 3.4 points (95% CI, 1.4 to 5.4), the DISCOVER-2 study reported an LS mean difference of 4.0 (95% CI, 2.5 to 5.5), and the COSMOS study reported an LS mean difference of 3.6 (95% CI, 1.7 to 5.4) for guselkumab every 8 weeks versus placebo. This outcome was not controlled for multiple testing (i.e., the type I error rate was not controlled).

Radiographic progression was a major secondary outcome in the DISCOVER-2 study. Progression was assessed using the modified van der Heijde-Sharp score, which ranges from 0 (best) to 528 (worst) and is the sum of the joint erosion score and the joint space narrowing score. At 24 weeks, the study failed to detect a statistically significant difference between guselkumab every 8 weeks and placebo in the change from baseline in van der Heijde-Sharp score; however, the duration of the trial may have been insufficient to detect a difference.

Harms Results

The frequency of adverse events was generally similar between groups in all trials, with 42% to 54% of patients in the guselkumab every 8 weeks groups and 41% to 60% of patients in the placebo groups reporting 1 or more adverse events during the 24-week treatment period. Nasopharyngitis (4% to 13%), upper respiratory tract infection (2% to 5%), and increased alanine aminotransferase (2% to 6%) were the most common adverse events in the guselkumab every 8 weeks groups, with a comparable frequency of these events reported in the placebo groups. Generally, the frequency of infections was similar in the guselkumab every 8 weeks groups (16% to 26%) and the placebo groups (18% to 25%) across trials, and few serious infections were reported (0% to 0.5% in the guselkumab every 8 weeks groups).

The frequency of serious adverse events ranged from 1% to 4% in the guselkumab every 8 weeks groups and 3% to 4% in the placebo groups. No specific serious adverse events were reported in more than 1 patient per treatment group. Adverse events that resulted in treatment discontinuation were generally low and similar between groups (1% to 3%). In the DISCOVER-1 study, 1 patient in the placebo group died due to cardiac failure. No other deaths were reported in the first 24 weeks of the trials.

Critical Appraisal

The risk of bias related to randomization and treatment allocation concealment was rated as low for all studies, and, in general, the patient characteristics and co-interventions appeared to be balanced between groups at baseline. The trials were double blind and took steps to maintain blinding of patients and investigators. Joint assessments were conducted by an independent rater, who was not otherwise involved in the trial. Therefore, the risk of bias in the measurement of the outcomes was low for all trials. The frequency of withdrawals in all trials was low and similar between groups, so there is a low risk of bias due to missing outcome data. The full analysis set, which excluded only 1 randomized patient in the DISCOVER-2 trial, was used for all efficacy outcomes, so the analyses were appropriate for estimating the effect of assignment to the intervention.

In all trials, the primary and other dichotomous end points were analyzed using a Cochran-Mantel-Haenszel test that was stratified by randomization stratification factors, with missing data imputed as nonresponders. The DISCOVER trials used an adjusted ANCOVA model, and the COSMOS study used an unadjusted mixed models for repeated measures model to analyze continuous outcomes. Missing data were imputed under the missing at random assumption, which may not hold true, but this was not thought to be a major source of bias. Efficacy analyses were based on the composite estimand, where any patients who met treatment failure criteria were considered nonresponders for binary end points, or as no change from baseline for continuous measures. Treatment failure criteria included early study withdrawal or discontinuation of the study drug, or initiation of new treatments for PsA. This estimand, which considers any treatment failure end points to be an unfavourable outcome, may be a more conservative estimate of treatment effects. Of note, the COSMOS study incorrectly assigned 20 patients to early escape, despite these patients not having met the escape criteria. Although the sponsor did sensitivity analyses to explore the impact of this error, these analyses cannot fully address the potential bias. The type I error rate was controlled for the primary and selected secondary outcomes in all studies. However, there were several outcomes of interest to this review that were not controlled for multiplicity; thus, these data should be interpreted with caution given the potential for inflated type I error rate. Randomization was not stratified by the presence of psoriasis, enthesitis, dactylitis, or axial disease; thus, interpretation of the results for these outcomes should consider the possibility of imbalances in baseline demographic and disease characteristics between treatment groups in these subpopulations. The primary outcome was ACR 20 response, but according to the clinical expert, this represents the minimum level of improvement that may be relevant to patients. In practice, the goal of therapy is to achieve higher levels of response.

Although the trials were 48 to 100 weeks in duration, the comparative period was limited to 24 weeks for this chronic condition. For outcomes such as radiologic changes, the duration of treatment may have been insufficient to detect the impact of guselkumab. Moreover, none of the trials included an active control group; thus, direct evidence comparing guselkumab to other DMARDs available in Canada is not available.

With regards to external validity, the clinical expert did not identify any substantial limits to generalizability based on the patient population enrolled. The guselkumab every 8 weeks dosing regimen used in the trials was consistent with the Health Canada–recommended dose, and the expert stated that concomitant utilization of conventional DMARDs was similar to what may be expected in practice. The expert did note that the use of oral corticosteroids in the DISCOVER trials (i.e., 14% to 20%) was higher than would be expected in Canada. The use of a placebo comparator as an add on to conventional DMARDS and NSAIDS is

not consistent with Canadian practice for patients whose disease has demonstrated an inadequate response to conventional or biologic DMARDs. The trials excluded patients who had previously been treated with other biologics besides TNF inhibitors; thus, the efficacy in patients with intolerance or inadequate response to other biologics, such as JAK or other IL inhibitors, is not known.

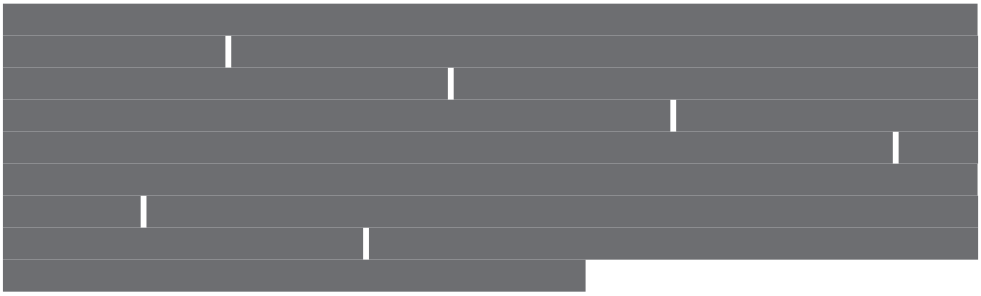
Indirect Comparisons

Description of Studies

The sponsor conducted an NMA of RCTs that assessed the comparative efficacy and safety of guselkumab and 13 other biologic DMARDs for the short-term treatment of acute PsA. The indirect comparison was based on a systematic literature review, and 34 RCTs provided data to inform the Bayesian NMA. Analyses were conducted for the overall PsA population, with subgroup analyses restricted to patients who were biologic-naive or biologic-experienced. Treatment duration was 12 to 24 weeks.

One other NMA was identified by CADTH through a literature search. The NMA by McInnes et al. (2022) evaluated the efficacy and safety of licensed and unlicensed biologic DMARDs for patients with active PsA. A total of 46 RCTs, which were identified through a systematic review, were included in the Bayesian analyses. The NMA included 19 biologics with outcomes assessed at 12 to 26 weeks.

Efficacy Results



The results for ACR 20 and PASI 90 response in the NMA by McInnes et al. (2022) were largely consistent with the findings of the sponsor-submitted NMA.

Harms Results

No comparative safety data for guselkumab were reported in the NMA by McInnes et al. (2022).

Critical Appraisal

Although the sponsor-submitted indirect comparison was based on a systematic review, [redacted] RCTs were excluded from the NMA, and the criteria for selecting trials or outcomes for analysis were not stated. Heterogeneity in patient and study characteristics was identified and it is unclear if the transitivity assumption has been met. The authors of the NMA attempted to

address potential variability in effect modifiers by using a baseline-risk adjusted model, but it is unclear if these effect modifiers have the same level of effect on the active arms. Given that it is unclear to what extent placebo response is an adequate proxy for specific characteristics or effect modifiers, uncertainty remains in these analyses. Subgroup analyses based on prior treatment exposure were conducted to create more homogenous patient populations, but some of these analyses included data from a limited number of trials, and often showed substantial uncertainty, with wide credible intervals. There were no subgroup or sensitivity analyses conducted to explore the potential impact of differences in the timing of outcome assessment, duration of disease, background therapies, or year of study.

ACR and PASI response were analyzed using an ordinal model, which assumed the relative treatment effects were the same for each response level. Thus, although data were reported separately for each response level, the inferences for each comparison are the same across the ACR 20, 50, and 70 levels, or PASI levels. It is not clear if this assumption of the model holds true (i.e., whether relative treatment effects are consistent across response levels), given that data were pooled for different time points. No sensitivity analyses were run to examine the impacts of this assumption.

In the sponsor-submitted NMA, there was limited ability to assess the consistency between direct and indirect evidence as there were few closed loops (only [redacted] head-to-head studies), and the statistical tests for inconsistency are generally underpowered. Furthermore, most of the contributing trials were judged to be at high or unclear risk of bias in at least 1 domain.

Issues with heterogeneity in patient and study characteristics, lack of ability to assess consistency, and potential bias in the included RCTs were also identified as limitations of the NMA by McInnes et al. (2022).

The indirect evidence was limited to short-term efficacy and safety; thus, longer-term comparative effects are uncertain.

Other Relevant Evidence

Description of Studies

Efficacy and safety data were available for the uncontrolled extension phase of the DISCOVER-1 (52 weeks), DISCOVER-2 (100 weeks), and COSMOS (48 weeks) trials. Descriptive results for patients who received guselkumab 100 mg every 8 weeks have been summarized in this section, including patients from the placebo group in the COSMOS study who crossed over to guselkumab every 8 weeks.

Efficacy Results

The extension phase data suggest that treatment effects may be maintained in patients who remain on guselkumab every 8 weeks therapy for 48 to 100 weeks. In the DISCOVER-1 trial, 76 of 112 patients (68%), and in the COSMOS trial, 120 of 172 patients (70%) achieved ACR 20 response at week 48 or 52. In the DISCOVER-2 study, 85 of 234 (79%) patients achieved ACR 20 response at week 52, and 183 of 223 (82%) at week 100. PASI 100 response was reported by 36 out of 75 (48%) patients in the DISCOVER-1 trial (week 52), 94 out of 169 (57%) in the DISCOVER-2 trial (100 weeks), and 80 out of 121 (66%) in the COSMOS trial (48 weeks).

Harms Results

During the extension period, 31% to 72% of patients reported 1 or more adverse events, 3% to 9% reported a serious adverse event, and 1% to 3% stopped treatment due to adverse events. No deaths were reported. Infections were reported in 43% of patients in the DISCOVER-1 study and in 29% and 38% of patients at week 52 and 100 of the DISCOVER-2 study. Over the 48-week treatment period of the COSMOS study, 22% of patients who received guselkumab every 8 weeks experienced an infection.

Critical Appraisal

Limitations of the extension study include selection bias and lack of a control group. Data were only available as descriptive statistics, and since there were no comparator groups, the interpretation of the results is limited. The outcomes were based on observed case data with no imputation for missing data and reflect treatment effects in patients who continue on therapy. As such, the results may overestimate the response in the broader population, as patients who drop out are more likely to have unfavourable outcomes or poor tolerance to therapy.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	• Adult patients with PsA who have had an inadequate response to standard therapies, defined as cDMARDs, apremilast, and/or NSAIDs. • The sponsor also presented subgroup analyses for: • adults with PsA who are bio-naive • adults with PsA who are bio-experienced
Treatment	Guselkumab, alone or in combination with a cDMARD
Dosing regimen	100 mg at weeks 0 and 4 and every 8 weeks thereafter
Submitted price	$3,059.74 per 100 mg/mL prefilled syringe or patient-controlled injector
Treatment cost	$21,418 per patient in the first 52 weeks, and $19,888 per patient per year thereafter
Comparators	• Mixed population: adalimumab, apremilast, certolizumab, etanercept, golimumab, infliximab, ixekizumab, secukinumab, upadacitinib, ustekinumab, and BSC (i.e., cDMARDs and supportive or palliative care) • Bio-naive: adalimumab, apremilast, etanercept, golimumab, infliximab, ixekizumab, secukinumab, upadacitinib, ustekinumab, and BSC • Bio-experienced: ixekizumab, secukinumab, upadacitinib, ustekinumab, and BSC
Perspective	Canadian publicly funded health care payer
Outcome	QALYs

Component	Description
Time horizon	Lifetime (53 years)
Key data sources	The DISCOVER-1, DISCOVER-2, and COSMOS trials informed the efficacy of guselkumab. Sponsor-submitted NMAs for each population informed the comparator efficacy.
Key limitations	• Relative treatment effects are uncertain as the mixed population analysis combines heterogeneous populations (bio-naive and bio-experienced) without regard to prevalence or proportions among comparator trials. As recommended by the CADTH Economic Guidelines, when a stratified analysis is conducted, rather than calculating the mean result (i.e., the ICER) over the entire population, the appropriate estimate of the overall result is determined by weighting the estimates for each subgroup by their respective prevalence. • Due to the lack of direct evidence and the limitations of the submitted NMA, the relative treatment effects among biologic comparators are uncertain in the short and long term. • The modelled long-term discontinuation rates were based on a naive comparison, and the use of BSC as the only subsequent therapy overemphasizes the impact of these differences. • Disease-related resource use is uncertain and likely double counts resource use such as health care provider visits and labs tests in some instances. • The treatments modelled were not reflective of current clinical practice due to the inclusion of apremilast and the exclusion of several relevant comparators (i.e., the TNF inhibitors) in the bio-experienced population.
CADTH reanalysis results	• CADTH reanalyses assumed equal discontinuation rates between biologic comparators, removed double-counted resource use, removed apremilast as a comparator, and did not consider the mixed population analysis. • The results of CADTH reanalyses indicate that guselkumab was dominated by (i.e., was more costly and less effective than) multiple comparators in both the bio-naive and bio-experienced populations. • Based on the CADTH reanalyses, a price reduction of 20% to 42% is required for guselkumab to move onto the cost-effectiveness frontier, based on publicly available list prices for comparator treatments.

bio-experience = those who have had an inadequate response or were intolerant to a biologic therapy; bio-naive = those who are biologic-naive and have had an inadequate response to standard therapies; BSC = best supportive care; cDMARD = conventional disease-modifying antirheumatic drug; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; NSAID = nonsteroidal anti-inflammatory drug; PsA = psoriatic arthritis; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the analysis assumes only patients who would otherwise receive an alternate biologic will access guselkumab, which implies that guselkumab will be reimbursed in a manner similar to other biologics; the proportion of patients with PsA who will use biologics is uncertain; the market uptake of guselkumab is uncertain; biosimilar use was underestimated; the Non-Insured Health Benefits population was inappropriately calculated; and the estimation of patients in the induction phase of biologic use was inappropriate. CADTH reanalyses included assuming 100% subsequent entry biologic use where available, correcting the Non-Insured Health Benefits population estimates, and assuming that 100% of incident (new) patients and 16.5% of prevalent patients (pre-existing) were in an induction phase of their biologic during each year of the model.

CADTH reanalyses suggest that if guselkumab is reimbursed in a similar manner to other biologic drugs for the treatment of PsA, its reimbursement would be associated with a budgetary increase of $1,044,542 in year 1, $1,422,986 in year 2, and $2,244,168 in year 3, for a 3-year total incremental cost of $4,711,697. Should guselkumab be reimbursed for its full Health Canada indication of adults with active PsA, the budgetary impact would be

substantially higher. When price reductions of 20% and 42% as estimated for patients who are bio-naive and bio-experienced in the CADTH cost-utility analysis reanalysis, the 3-year incremental budget impact would be a cost of $874,960 and a savings of $3,312,951, respectively.

CADTH was unable to revise the model to incorporate the potential that the availability of guselkumab (based on its Health Canada indication) may increase the biologic market for PsA, nor revise market uptake and displacement by guselkumab; thus, the budget impact of reimbursing guselkumab is uncertain. Additionally, the actual prices paid by public drug plans for the comparators is unknown.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: September 27, 2022

Regrets: Three expert committee members did not attend.

Conflicts of interest: None