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Reimbursement Recommendation

Guselkumab (Tremfya)

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis

Sponsor: Janssen Inc.

Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Tremfya?

Canada's Drug Agency (CDA-AMC) recommends that Tremfya be reimbursed by public drug plans for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Tremfya should only be covered for a patient population similar to that eligible for other advanced therapies for UC (e.g., biologics, sphingosine 1-phosphate receptor modulators, or Janus kinase [JAK] inhibitors) currently reimbursed by public drug plans.

What Are the Conditions for Reimbursement?

Tremfya should only be reimbursed if it is prescribed by a physician experienced in the diagnosis and management of UC, and if it is not used in combination with other advanced therapies for UC. A patient's disease must respond to treatment in the first 24 weeks of starting Tremfya to continue receiving the drug. The cost of Tremfya should not exceed the drug program cost of treatment with the least costly advanced therapy reimbursed for the treatment of UC.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that more patients who were treated with Tremfya showed clinical remission and response and endoscopic improvement than patients who received placebo, and this benefit was maintained for up to 44 weeks.
- Tremfya met some of the needs identified as important to patients, including being an additional treatment option that can improve symptoms and health-related quality of life (HRQoL). Additionally, more patients who were treated with Tremfya had corticosteroid-free clinical remission than those who received placebo, which is important to patients and clinicians.
- Based on the CDA-AMC 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 versus other relevant advanced therapies reimbursed for the treatment of adults with moderately to severely active UC.

Summary

- Based on public list prices, Tremfya is estimated to cost the public drug plans approximately $10 million over the next 3 years.

Additional Information

What Is UC?

UC is an inflammatory bowel disease that causes inflammation and ulcers in the lining of the large intestine and rectum. Signs and symptoms include blood in stool, frequent diarrhea, loss of appetite, strong urge to use the bathroom without necessarily having a bowel movement, abdominal pain, and rectal bleeding. UC occurs in 414 per 100,000 people in Canada.

Unmet Needs in UC

The available treatment options do not work in all patients with UC. Treatment response varies across patients and response to treatment may stop after prolonged use; thus, patients have noted a need for other treatments that reduce the severity of symptoms, help achieve sustained disease remission, reduce repetitive use of corticosteroids, and improve HRQoL.

How Much Does Tremfya Cost?

Treatment with Tremfya is expected to cost between $23,016 and $39,913 per patient per year in year 1 and between $19,957 and $39,913 per patient per year in subsequent years, depending on the frequency with which maintenance doses are received.

Recommendation

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

Rationale for the Recommendation

Two phase III, double-blind, placebo-controlled trials (the QUASAR induction trial, N = 701; and the QUASAR maintenance trial, N = 568) demonstrated that guselkumab induction (100 mg) and maintenance (100 mg and 200 mg) treatment, compared to placebo, resulted in added benefit in clinical remission, endoscopic healing, clinical response and maintenance of clinical response, corticosteroid-free clinical remission (maintenance only), and HRQoL in adults with moderately to severely active UC who had experienced an inadequate response to, or were unable to tolerate, conventional or advanced therapy. For clinical remission after 12 weeks of induction treatment and after 44 weeks of maintenance treatment, the estimated between-group difference was 14.9% (95% confidence interval [CI], 9.9% to 19.9%), and 25.2% (95% CI, 16.4% to 33.9%) for the 100 mg dose and 29.5% (95% CI, 20.9% to 38.1%) for the 200 mg dose, respectively. For endoscopic healing after 12 weeks of induction treatment and after 44 weeks of maintenance treatment, the estimated between-group difference was 16.0% (95% CI, 10.5% to 21.4%) and 29.5% (95% CI, 20.7% to 38.3%) for the 100 mg dose and 31.1% (95% CI, 22.5% to 39.8%) for the 200 mg dose, respectively. For clinical response at 12 weeks and maintenance of clinical response at 44 weeks, the estimated between-group difference was 33.8% (95% CI, 26.9% to 40.7%) and 33.6% (95% CI, 24.5% to 42.7%) for the 100 mg dose and 30.7% (95% CI, 21.5% to 40.0%) for the 200 mg dose, respectively. For corticosteroid-free clinical remission at 44 weeks, the estimated between-group difference was 25.7% (95% CI, 17.0% to 34.5%) for the 100 mg dose and 29.0% (95% CI, 20.5% to 37.6%) for the 200 mg dose. For HRQoL, measured via remission per Inflammatory Bowel Disease Questionnaire (IBDQ) score after 12 weeks of induction treatment and after 44 weeks of maintenance treatment, the estimated between-group difference was 21.9% (95% CI, 14.9% to 29.0%) and 26.3% (95% CI, 16.8% to 35.7%) for the 100 mg dose and 25.9% (95% CI, 16.5% to 35.4%) for the 200 mg dose.

Patients identified a need for accessible and effective treatment options that reduce symptoms and achieve sustained remission, including corticosteroid-free remission, and improve HRQoL. CDEC concluded that guselkumab met some important needs identified by patients — such as sustained clinical remission, endoscopic healing, clinical response, and improved HRQoL — and that it represents an additional advanced therapy option.

At the sponsor-submitted price for guselkumab and publicly listed price for comparators, guselkumab was more costly than most other reimbursed advanced therapies for adult patients with moderately to severely active UC who have experienced an inadequate response to or inability to tolerate conventional or advanced therapy. Direct comparative evidence to other advanced therapies was not identified, and indirect evidence was insufficient to draw conclusions regarding the relative efficacy of guselkumab compared with other

advanced therapies. As such, the total drug cost of guselkumab should not exceed the total drug cost of the least costly relevant advanced therapy reimbursed in this patient population.

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 plans for the reimbursement of other advanced drugs for the treatment of moderately to severely active UC.	The QUASAR induction and maintenance trials demonstrated that induction and maintenance treatment with guselkumab resulted in a clinical benefit in patients with moderately to severely active UC who had experienced an inadequate response to or were unable to tolerate conventional therapy (i.e., 6-mercaptopurine, azathioprine, or corticosteroids) or advanced therapy (i.e., TNF antagonists, vedolizumab, or tofacitinib).	The definitions of "moderately to severely active UC" should align with those used for other reimbursed advanced therapies. Advanced therapies include biologics, JAK inhibitors, and sphingosine 1-phosphate receptor modulators.
Renewal		
2. The patient must have achieved clinical response to guselkumab induction therapy at 24 weeks of treatment initiation to continue to maintenance therapy. Clinical response targets should be based on the criteria used by each of the public drug plans for reimbursement of other biologic drugs for the treatment of moderately to severely active UC in adults who have had an inadequate response or loss of response to other treatment options (conventional therapy or advanced therapies).	This is to ensure patients are benefiting from guselkumab therapy. The QUASAR induction trial assessed the efficacy and safety of guselkumab after 12 weeks induction treatment, and patients who achieved clinical response entered the maintenance trial. Patients who had not experienced a response to treatment at week 12 were allowed to continue guselkumab treatment and were re-evaluated for response at week 24. The clinical experts indicated that 24 weeks would be a reasonable time frame to assess the efficacy of guselkumab induction therapy, as some patients may have disease that is late to respond. This is aligned with results of the QUASAR induction trial, in that more than half of the patients (55.2%; n = 69) whose disease did not respond after 12 weeks of treatment achieved clinical response at week 24.	A modified Mayo score that requires an endoscopy was used in the QUASAR induction and maintenance trials to determine clinical response. Given the invasive nature of an endoscopy and the limitations associated with timely access and associated costs of health care resources in Canada, CDEC considered it appropriate to leave the determination of clinical response up to the judgment of the treating physician.
3. Assessment for renewal after the first assessment of treatment response should be performed every year. The patient's disease must maintain clinical response to therapy for them to continue receiving guselkumab.	Patients whose disease loses response to guselkumab are no longer benefiting from treatment.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
4. Guselkumab should be prescribed by clinicians with expertise in the diagnosis and management of UC.	This is to ensure that guselkumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Guselkumab should not be reimbursed when used in combination with other advanced therapies for UC, such as biologics, sphingosine 1-phosphate receptor modulators, or JAK inhibitors.	There is no evidence to support the use of guselkumab in combination with biologic therapy, sphingosine 1-phosphate receptor modulators, or JAK inhibitors for UC.	—
Pricing		
6. The price of guselkumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly available relevant advanced therapy reimbursed for the treatment of adult patients with moderately to severely active UC.	The comparative efficacy and safety of guselkumab relative to other relevant advanced therapies available for moderately to severely active UC is uncertain due to a lack of head-to-head evidence and limitations with the sponsor's NMA, which precluded the Clinical Review by CDA-AMC from being able to draw conclusions regarding the relative efficacy and safety of guselkumab. As such, there is insufficient evidence to justify a cost premium for guselkumab over the least costly relevant advanced therapy reimbursed for adult patients with moderately to severely active UC.	—

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; JAK = Janus kinase; NMA = network meta-analysis; UC = ulcerative colitis.

Discussion Points

- **Unmet need**: Patients and clinicians identified a need for additional advanced therapy options that are effective. The clinical experts consulted by CDA-AMC indicated that, in clinical practice, some patients experience an inadequate response or loss of response to currently available advanced therapies and require alternative treatments. CDEC noted that, currently, there are many advanced therapies available for UC. Based on the submitted evidence, CDEC concluded that guselkumab does not meet the unmet needs identified by patients when compared to other advanced therapies; however, the evidence is supportive of guselkumab as an additional effective treatment option for patients with moderately to severely active UC, specifically in those who have disease that has failed to respond to conventional or advanced therapy, as per the QUASAR trial populations.
- **Efficacy and safety:** CDEC highlighted that the evidence from the QUASAR induction and maintenance trials was of high certainty, per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment that guselkumab results in a clinically important improvement for the outcomes of clinical remission, endoscopic healing, clinical response and

maintenance of clinical response, corticosteroid-free clinical remission (maintenance only), and HRQoL measured by IBDQ remission after12 weeks of induction treatment and after 44 weeks of maintenance treatment when compared with placebo. In both trials, serious treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation of treatment, notable harms (i.e., infections), and deaths were infrequent and similar across the treatment groups. CDEC agreed with the clinical experts that there were no new safety signals identified and that the safety of guselkumab was consistent with the known safety profile of the drug class.

- **Indirect evidence:** Direct evidence comparing guselkumab with other advanced therapies was not submitted. CDEC discussed the indirect evidence from the sponsor-submitted network meta-analysis (NMA). In the NMA, the results for clinical remission and clinical response were subject to uncertainty due to imprecision and heterogeneity in the populations and studies that could not be accounted for in the analyses. Due to the limitations, CDEC could not draw definitive conclusions about the comparative efficacy of guselkumab relative to adalimumab, infliximab, tofacitinib, upadacitinib, mirikizumab, vedolizumab, etrasimod, ozanimod, or ustekinumab in adults with moderately to severely active UC whose disease has failed to respond to conventional or advanced therapy. No safety outcomes were included in the NMA; therefore, CDEC could not draw any conclusions about the safety of guselkumab compared to relevant comparators.
- **Induction and maintenance regimens:** CDEC discussed the variable length of induction therapy for guselkumab. In the QUASAR induction trial, patients in the guselkumab group who had disease that did not respond to 12-week induction dosing received an additional 12 weeks of induction therapy. After a total of 24 weeks of induction therapy, 55.2% of patients (n = 69) whose disease did not respond after 12 weeks of treatment achieved clinical response at week 24. CDEC also discussed the 200 mg maintenance dose option that was compared to placebo in the QUASAR maintenance trial, and concluded that there was no evidence of a dose response between the guselkumab 100 mg and 200 mg groups. This information may prove useful for payers when assessing the total cost of treatment to ensure guselkumab is no more costly than the least costly relevant comparator (i.e., advanced therapy) reimbursed for adults with moderately to severely active UC.

Background

Inflammatory bowel disease (IBD) comprises a group of diseases characterized by chronic, recurrent, progressive inflammation of the gastrointestinal (GI) tract. There are 2 main types of IBD: Crohn disease (CD) and UC. UC is a chronic disease characterized by inflammation and ulcers in the mucosal layer of the large intestine (colon), typically beginning at the rectum (anus), progressing upwards, and in some cases affecting the entire colon. The cause of UC remains uncertain, but a combination of genetic and environmental factors contribute to immune dysregulation and upregulation in response to micro-organisms in the GI tract. Patients with UC present with the following symptoms: blood in the stool with mucus, frequent diarrhea, loss of appetite, and tenesmus (strong urge to use the bathroom without necessarily having a bowel movement), in addition to abdominal pain, rectal bleeding, and weight loss. UC generally develops

in young adulthood and persists throughout life, marked by periods of spontaneous remission and relapse. UC has a worldwide annual incidence rate of 1.2 to 20.3 cases per 100,000 people and a prevalence of 7.6 to 246.0 cases per 100,000 people. The prevalence of UC in Canada in 2023 was estimated to be 414 per 100,000. It is estimated that 32% to 46% of Canadians with UC have moderate disease, and 13% to 14% have severe disease.

UC can be further classified in clinical practice based on severity: mild, moderate, or severe disease, depending on the specific index score used (Truelove and Witts Severity Index, Mayo Clinic score, or Montreal Classification). While most patients have a mild to moderate disease course, about 10% to 15% experience an aggressive course of UC. Relapse is common, with the cumulative risk of relapse being 70% to 80% at 10 years. Achieving endoscopic healing earlier may be associated with reduced risk of future colectomy. The chronic nature of UC has a considerable impact on patients' HRQoL, including psychological, physical, sexual, and social domains of HRQoL, due to chronicity of symptoms such as urgency and frequency, and incontinence.

The reimbursement criteria requested for guselkumab is for the treatment of adult patients with moderately to severely active UC. In general, the reimbursement request aligns with the proposed Health Canada indication, except that the proposed indication is not limited to patients who have inadequate response to or are unable to tolerate conventional or advanced therapy.

Guselkumab is a human IgG1-lambda monoclonal antibody. The recommended induction dosage is 200 mg of guselkumab administered by IV infusion over a period of at least 1 hour at week 0, week 4, and week 8. The recommended maintenance dosage is 100 mg of guselkumab administrated by subcutaneous (SC) injection at week 16 and every 8 weeks thereafter after completion of induction dosing. A dose of 200 mg administered by SC injection at week 12 and every 4 weeks thereafter may be considered for patients who do not show an adequate therapeutic response to guselkumab, or according to clinical judgment.

Sources of Information Used by the Committee

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

- a review of 2 phase III, double-blind, randomized controlled trials in adults with moderately to severely active UC
- patients' perspectives gathered by 2 patient group(s), Crohn's and Colitis Canada and the Gastrointestinal (GI) Society
- input from public drug plans that participate in the CDA-AMC reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with UC
- a review of the indirect evidence from 1 indirect treatment comparison submitted by the sponsor
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Two patient groups, Crohn's and Colitis Canada and the GI Society, provided input for guselkumab for the treatment of UC. Patient input from Crohn's and Colitis Canada was gathered from an online survey conducted in 2022. Patient input from the GI Society contained questionnaires and interviews collected through several surveys conducted in 2024, 2023, 2022, 2020, 2018, and 2015, and 1 focus group conducted in 2022.

When asked what UC-related complications patients had been experiencing currently or within the past year, the most frequently reported complications by respondents in the Crohn's and Colitis Canada input were mental health and stress (65%), followed by joint inflammation and arthritis (51%), anal fissures and hemorrhoids (40%), anemia (33%), and skin conditions as well as malnutrition and weight loss (both approximately 30%). Diarrhea, bowel urgency, incontinence, abdominal pain, fever, rectal bleeding, and nausea were reported by respondents as the common symptoms of UC in the GI Society input. Patients from the GI Society input added that sustained remission or treatment response was more important than relieving any 1 symptom.

In the surveys conducted by the GI Society, 33% of respondents in 2020 and 29% of respondents in 2024 believed that their IBD was not well controlled by their current medications. While the GI Society indicated that corticosteroids are helpful to reduce inflammation in moderate to severe cases, they also emphasized that these medications are appropriate for short-term treatment only because they are generally not well tolerated and can have potentially serious side effects. Half of the respondents in the Crohn's and Colitis Canada input indicated that systemic steroids are or were a burden in the management of UC, particularly among those with moderate to severe forms of UC, and among women. According to respondents from the Crohn's and Colitis Canada input who indicated that managing medication use is important, having enough treatment options, understanding side effects of treatment, and minimizing steroid use were the most important aspects in the management of UC. No patients from any of the groups had experience with the drug under review.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts indicated that the treatment goals for patients with moderately to severely active UC are to induce and maintain clinical and endoscopic remission. The experts noted that first-line therapy typically includes oral mesalamine plus corticosteroids, used for rapid achievement of clinical remission. Corticosteroids are not used in maintenance therapy and are avoided as a recurrent "rescue" medication, given a wide array of adverse effects common to their use. The experts noted that although mesalamine is effective for some patients, it is ineffective in those with more severe disease; therefore, these patients require an alternative, advanced therapy to maintain remission. The experts noted that the challenge with currently available therapies for UC in Canada is that a portion of patients will not respond to advanced therapy, and in patients who respond initially, most lose response after a period of symptom relief. As such, in many patients, dose escalation and trying several types of therapies are needed to maintain response

and meet longer-term treatment goals. The clinical experts pointed out that multiple drug failures and ongoing progressive disease activity may lead to adverse consequences, including surgery to remove the entire colon. The experts noted that there is also a gap in available oral therapies, as most current therapies are administered intravenously or subcutaneously. The clinical experts indicated that a clear sequence of medications that is optimal to treat moderate to severe UC is not yet established. In the clinical experts' opinion, guselkumab should be available as a first-line treatment option, and failure of a previous therapy should not be a criterion to access the drug. The clinical experts indicated that patients best suited for guselkumab would be those with moderately to severely active UC. The experts highlighted that patients would be identified based on clinical examination and judgment, including history of symptoms, biomarker evaluation, endoscopic assessment, and histopathological evaluation. The clinical experts indicated that, in clinical practice, a combination of clinical scoring systems (e.g., Mayo and partial Mayo scores), endoscopic outcomes, histopathological evaluation, and patient-reported HRQoL scores are used to determine whether a patient's disease is responding to or progressing on treatment. The experts noted that patients starting a new advanced therapy should have a clinical follow-up assessment within 14 to 16 weeks of initiating therapy. The clinical experts indicated that treatment with guselkumab should be discontinued if patients do not respond to treatment, and if patients experience disease progression (e.g., ongoing symptoms or symptom escalation) while on maintenance therapy. The experts noted that disease progression while on guselkumab maintenance therapy would not necessarily mean the medication needs to be discontinued, and it would require further clinical assessment to determine if discontinuation is warranted.

Clinician Group Input

No clinician group input was received by CDA-AMC for this review.

Drug Program Input

The clinical experts consulted by CDA-AMC provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The sponsor conducted a systematic review, ultimately identifying 3 trial records, each being a part of the QUASAR program: induction study 1, induction study 2, and the maintenance study. They were double-blind, placebo-controlled, parallel-group, multicentre studies. The study drug was not compared to a relevant comparator, as placebo was used. Comparator drugs include ustekinumab, mirikizumab, golimumab, vedolizumab, upadacitinib, adalimumab, infliximab, tofacitinib, ozanimod, and etrasimod, most of which were included in the indirect comparison studies. Of note, the sponsor is currently conducting the ASTRO trial to evaluate the efficacy of guselkumab SC induction compared to placebo in participants with moderately to severely active UC.	This is a comment from the drug plans to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
Not all relevant comparators are currently listed under drug plans. Some recommendations are recent, and some negotiations are ongoing, and this also varies by jurisdiction.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
The studies included adult patients with moderately to severely active UC, defined as a baseline modified Mayo score of 4 to 9, and a Mayo Rectal Bleeding subscore of ≥ 1. Is this the most appropriate scoring tool for identifying eligible patients for treatment with guselkumab in current clinical practice?	CDEC agreed with the clinical experts that the Mayo score is an appropriate tool to identify eligible patients for treatment with guselkumab. The clinical experts noted that the Mayo score is commonly used in clinical practice when assessing patients with UC.
The studies excluded patients with a presence or history of fistula. Should the use of guselkumab be avoided in these patients? Are there any other exclusions listed in the studies that would be considered as contraindications to treatment with guselkumab?	CDEC agreed with the clinical experts that guselkumab should not be used in patients with a presence or history of fistula. The clinical experts indicated that once a patient has developed fistulizing disease, they are no longer classified as having UC.
ADT is considered to be treatment with 1 or more TNF antagonists, vedolizumab, or tofacitinib at a dose approved for the treatment of UC. Are the prior treatments listed in the inclusion criteria appropriate to require in the real-world setting for eligibility of initiation of guselkumab therapy?	In the clinical experts' opinion, guselkumab should be available as a first-line treatment option for patients with UC, given that the induction and maintenance trials included patients who were ADT-naie and who had experienced ADT failure. They also confirmed that the list of prior advanced therapies (i.e., TNF antagonists, vedolizumab, or tofacitinib) is appropriate and that these are currently available treatment options for UC. CDEC acknowledged the input from the clinical experts and noted that the QUASAR trials provided evidence for the use of guselkumab in patients with moderately to severely active UC who had experienced an inadequate response to or were unable to tolerate conventional or advanced therapy.
Consider alignment with reimbursement criteria of recently reviewed comparators (i.e., Omvoh, Rinvoq, Zeposia).	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
Consider alignment with renewal criteria of recently reviewed comparators (i.e., Omvoh, Rinvoq, Zeporia).	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for discontinuation of therapy	
The study defined loss of response as no longer satisfying the definition of clinical response. Clinical response considered a range of improvements with the minimal important difference being a ≥ 3 point decrease in either the Mayo score or the partial Mayo score. Does the definition of loss of response requiring a change in therapy align with this?	CDEC agreed with the clinical experts that a 2- to 3-point change or greater in the partial Mayo score would be a reasonable definition for loss of response.
Consider alignment with stopping criteria of recently reviewed comparators (i.e., Omvoh, Rinvoq, Zeposia).	This is a comment from the drug plans to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
Induction: Recommended dose of 200 mg IV infusion in weeks 0, 4, and 8. Maintenance: 1. Recommended dose of 100 mg SC at week 16 and every 8 weeks thereafter. 2. A dose of 200 mg SC at week 12 and every 4 weeks thereafter may be considered for patients who do not have an adequate therapeutic response to guselkumab, or according to clinical judgment. Note for CDEC: It would be helpful for drug plans to have some defined conditions for considering the 200 mg maintenance option. With the sponsor noting their current ASTRO study for SC induction with guselkumab, it is possible that the recommended induction dosing will change. In what scenarios would the 200 mg maintenance dosing option be prescribed? Participants with a loss of response to the 100 mg dose in the maintenance arm were eligible to receive the 200 mg dosing option beginning between maintenance weeks 8 and 32. Considering this, would this only be an option chosen in patients with inadequate response following induction, or would this also be an option if a patient were to begin showing a loss of effect on maintenance 100 mg every 8 weeks? Is there a time limit to increasing the dose?	The clinical experts noted that either of the following 2 examples would prompt them to prescribe the 200 mg maintenance dose option: • patients who have a severe Mayo score upon conducting an endoscopy or who are considered to have a higher disease burden • patients whose disease is not responding to the 100 mg dose at week 16 or week 20. CDEC agreed with the clinical experts that the option to use the 200 mg maintenance dose should be at the discretion of the treating physician.
The induction dosing will need to be administered by a trained health care professional in a hospital setting or infusion clinic. Training will be required for patients or caregivers administering the maintenance dosing.	This is a comment from the drug plans to inform CDEC deliberations.
Access to gastroenterologists can be limited in some areas.	This is a comment from the drug plans to inform CDEC deliberations.
Consider alignment with prescribing criteria of recently reviewed comparators (i.e., Omvoh, Rinvoq, Zeposia).	This is a comment from the drug plans to inform CDEC deliberations.
System and economic issues	
Given that there are several biologics, including biosimilars, currently listed as options on drug plans for UC, it is difficult to estimate how much of the market will be displaced by guselkumab. For CDEC consideration: Given that there are 2 maintenance dosing options, the price impact would be significant with 100 mg every 8 weeks compared to 200 mg every 4 weeks. It is unclear if the sponsor would make provisions for comparable pricing regardless of the option prescribed.	This is a comment from the drug plans to inform CDEC deliberations.
There are current PLAs in place for other biologics for UC and there are negotiations under way for additional biologics as well.	This is a comment from the drug plans to inform CDEC deliberations.

ADT = advanced therapy; CDEC = Canadian Drug Expert Committee; PLA = product listing agreement; SC = subcutaneous; UC = ulcerative colitis.

Clinical Evidence

Systematic Review

Description of Studies

Two pivotal, phase III, double-blind RCTs submitted by the sponsor were summarized in this report.

The QUASAR induction (N = 701) and maintenance (N = 568) studies met the inclusion criteria for the systematic review conducted by the sponsor. The objective of the induction study was to assess the efficacy and safety of guselkumab 200 mg IV as induction therapy or matching placebo administered at weeks 0, 4, and 8 in adults with moderately to severely active UC. The study enrolled patients who had demonstrated an inadequate response or were unable to tolerate conventional therapy (i.e., 6-mercaptopurine, azathioprine, or corticosteroids) or ADT (i.e., TNF antagonists, vedolizumab, or tofacitinib). Patients were required to have a modified Mayo score (MMS) of 4 to 9, a Mayo Rectal Bleeding score of 1 or more, and a Mayo Endoscopy subscore of 2 or more. Patients were eligible for the maintenance study if they had demonstrated a clinical response to guselkumab or placebo treatment at weeks 12 or 24. The objective of the maintenance study was to assess the efficacy and safety of guselkumab SC injection maintenance regimens (100 mg or 200 mg) or matching placebo in patients who had achieved clinical response with guselkumab IV induction. Patients received guselkumab 200 mg every 4 weeks, guselkumab 100 mg every 8 weeks, or placebo every 4 weeks starting at week 0 through week 44. In general, the proposed Health Canada indication and reimbursement request aligned with both study populations, except that the proposed indication is not limited to patients who have had an inadequate response to or are unable to tolerate conventional or advanced therapy. The outcomes most relevant to the CDA-AMC review included the primary outcome of clinical remission and secondary outcomes of endoscopic healing, clinical response and maintenance of clinical response, corticosteroid-free clinical remission (maintenance only), and HRQoL measured via IBDQ remission. For both studies, key baseline characteristics were generally balanced between treatment groups. Patients in the induction study were predominantly white (72.5%) and male (56.9%). The median age was 39.0 years (range, 18 years to 79 years), and the majority of patients were from Eastern Europe (42.2%), followed by “rest of world” (37.5%) and Asia (20.3%). The mean duration of disease was 7.5 years, and the mean baseline MMS was 6.9, with 64.5% of patients having severely active disease (i.e., MMS of 7 to 9) and 47.8% presenting with extensive disease. At baseline, 43.1% of patients were taking corticosteroids, 20.8% were taking immunomodulatory drugs, and 72.5% were taking oral aminosalicylates, with generally similar proportions of patients across the treatment groups. Among all patients, 93.2% had experienced an inadequate response or intolerance to corticosteroids and/or 6-mercaptopurine or azathioprine, or demonstrated corticosteroid dependence. Overall, 49.1% of patients had a history of ADT failure (i.e., anti-TNF, vedolizumab, or tofacitinib) and 50.9% had a history of ADT nonfailure. At induction baseline for the patients in the maintenance study, 40% were taking corticosteroids, 22.2% were taking immunomodulatory drugs (6-mercaptopurine or azathioprine, or methotrexate), 57.7% did not have a history of inadequate response or intolerance to ADT (of these, 94.2% were naive to ADT), and 42.3% had a prior inadequate response or intolerance to ADT. At maintenance baseline, the mean MMS was 2.5, 34.2% of patients were in clinical remission, and 39.1% had achieved endoscopic healing. For both studies, the primary analysis of

efficacy and safety outcomes were conducted in the full analysis set (FAS), which included patients who had received at least 1 (partial or complete) dose of the study intervention with a baseline MMS of 5 to 9.

Efficacy Results

For the induction study, the primary analysis of efficacy outcomes was conducted in the FAS, which included patients who had received at least 1 (partial or complete) dose of the study intervention with a baseline MMS of 5 to 9. For the maintenance study, the primary analysis of efficacy outcomes was performed in the randomized FAS among patients who had received treatment and who had a MMS of 5 to 9 at induction baseline. The following results are from the primary analyses.

Clinical Remission (Primary Outcome)

A greater proportion of patients in the guselkumab group (22.6%) compared with the placebo group (7.9%) achieved clinical remission at week 12, with an estimated adjusted between-group difference of 14.9% (95% CI, 9.9% to 19.9%; P < 0.001). The results for clinical remission were consistent across the prespecified subgroups of interest by those who were ADT-naive and those who had experienced ADT failure, in favour of guselkumab compared to placebo, with an adjusted between-group difference of 20.0% (95% CI, 11.6% to 28.3%) and 8.8% (95% CI, 3.4% to 14.3%), respectively.

A greater proportion of patients in the guselkumab 100 mg (45.2%) and 200 mg (50.0%) groups compared with the placebo group (18.9%) achieved clinical remission at week 44, with an estimated adjusted between-group difference of 25.2% (95% CI, 16.4% to 33.9%; P < 0.001) and 29.5% (95% CI, 20.9% to 38.1%; P < 0.001), respectively. The results for clinical remission were consistent across the prespecified subgroups of interest by those who were ADT-naive and those who had experienced ADT failure, in favour of guselkumab 100 mg and 200 mg compared to placebo. For the ADT-naive group, the adjusted between-group difference was 24.3% (95% CI, 12.0% to 36.5%) for patients taking guselkumab 100 mg and 28.8% (95% CI, 16.5% to 41.1%) for guselkumab 200 mg, respectively. For the ADT-failure group, the adjusted between-group difference was 30.4% (95% CI, 18.7% to 42.1%) for patients taking guselkumab 100 mg and 32.4% (95% CI, 21.1% to 43.7%) for guselkumab 200 mg.

Endoscopic Healing

A greater proportion of patients in the guselkumab group (26.8%) compared with the placebo group (11.1%) had endoscopic healing at week 12, with an estimated adjusted between-group difference of 16.0% (95% CI, 10.5% to 21.4%; P < 0.001).

A greater proportion of patients in the guselkumab 100 mg (49.5%) and 200 mg (51.6%) groups compared with the placebo group (18.9%) had endoscopic healing at week 44 in the maintenance study, with an estimated adjusted between-group difference of 29.5% (95% CI, 20.7% to 38.3%; P < 0.001) and 31.1% (95% CI, 22.5% to 39.8%; P < 0.001), respectively.

Clinical Response

Overall, 77.2% of patients (n = 325) achieved clinical response at week 12 or week 24, and among patients who were not in clinical response at week 12 (n = 125), 55.2% (n = 69) achieved clinical response at week 24. A greater proportion of patients in the guselkumab group (61.5%) compared with the placebo group

(27.9%) experienced clinical response at week 12, with an estimated adjusted between-group difference of 33.8% (95% CI, 26.9% to 40.7%; P < 0.001).

A greater proportion of patients in the guselkumab 100 mg (77.7%) and 200 mg (74.7%) groups compared with the placebo group (43.2%) maintained clinical response at week 44, with an estimated adjusted between-group difference of 33.6% (95% CI, 24.5% to 42.7%; P < 0.001) and 30.7% (95% CI, 21.5% to 40.0%; P < 0.001), respectively.

Corticosteroid-Free Clinical Remission

A greater proportion of patients in the guselkumab 100 mg (45.2%) and 200 mg (48.9%) groups compared with the placebo group (18.4%) achieved clinical remission and were corticosteroid-free at week 44 in the maintenance trial, with an estimated adjusted between-group difference of 25.7% (95% CI, 17.0% to 34.5%; P < 0.001) and 29.0% (95% CI, 20.5% to 37.6%; P < 0.001), respectively.

HRQoL Measured by IBDQ Remission

A greater proportion of patients in the guselkumab group (51.3%) compared with the placebo group (29.6%) achieved remission, per IBDQ score, at week 12, with an estimated adjusted between-group difference of 21.9% (95% CI, 14.9% to 29.0%; P < 0.001).

A greater proportion of patients in the guselkumab 100 mg (64.4%) and 200 mg (64.2%) groups compared with the placebo group (37.4%) achieved IBDQ-defined remission at week 44 in the maintenance trial, with an estimated adjusted between-group difference of 26.3% (95% CI, 16.8% to 35.7%; P < 0.001) and 25.9% (95% CI, 16.5% to 35.4%; P < 0.001), respectively.

Subgroup and Sensitivity Analyses of Key Secondary Outcomes

For both studies, the results for endoscopic healing, clinical response, corticosteroid-free clinical remission (maintenance only) and IBDQ-defined remission were consistent across the prespecified subgroups of interest by patients who were ADT-naive and patients who had experienced ADT failure, in favour of guselkumab compared to placebo (data not shown). For both studies, the results of the sensitivity analyses were consistent with the primary analyses.

Harms Results

In the induction study, 49.4% and 49.3% of patients reported at least 1 TEAE in the guselkumab and placebo groups, respectively. Over the 12-week treatment period, the most frequently reported TEAEs in the guselkumab and placebo groups were anemia (5.0% and 6.8%, respectively), COVID-19 (5.0% and 4.3%), headache (3.1% and 2.9%), and UC (2.4% and 8.2%). Of these TEAEs, a numerically higher proportion of UC was reported in patients taking placebo. In the maintenance study, 64.5%, 70.0%, and 68.2% of patients reported at least 1 TEAE in the guselkumab 100 mg, guselkumab 200 mg, and placebo groups, respectively. Over the 44-week treatment period, the most frequently reported TEAEs in the guselkumab 100 mg, guselkumab 200 mg, and placebo groups were UC (9.1%, 13.2%, and 29.7%, respectively) and COVID-19 (12.9%, 9.5%, and 14.1%). Of these TEAEs, a numerically higher proportion of UC was reported in patients taking placebo. In the induction study, 2.9% and 7.1% of patients reported at least 1 serious TEAE in the guselkumab and placebo groups, respectively. In the maintenance study, 2.7%, 6.3%, and 0.5% of

patients reported at least 1 serious TEAE in the guselkumab 100 mg, guselkumab 200 mg, and placebo groups, respectively. In the induction study, 1.7% and 3.9% of patients reported at least 1 TEAE leading to discontinuation of treatment in the guselkumab and placebo groups, respectively. In the maintenance study, 3.8%, 2.6%, and 6.8% of patients reported at least 1 TEAE leading to discontinuation of treatment in the guselkumab 100 mg, guselkumab 200 mg, and placebo groups, respectively. In the induction study, 1 death was reported in the guselkumab group and 2 deaths were reported in the placebo group. There were no deaths reported in the maintenance study. In the induction study, the incidence of notable TEAEs, which included infections and serious infections, were similar between groups. Infections were reported in approximately 15% of patients and serious infections were reported in less than 1% of patients in both groups. In the maintenance study, the incidence of notable infections and serious infections was also similar between groups. Infections were reported in approximately 32% of patients in all groups, and serious infections were reported in approximately 1% of patients in the guselkumab groups and no patients in the placebo group. No cases of active tuberculosis were reported in either study.

Critical Appraisal

Both the induction and maintenance studies were randomized, double-blind, placebo-controlled, parallel-group trials. Randomization and allocation concealment for both studies were performed using appropriate methodology via interactive web response system. Randomization stratification was prespecified and was based on relevant prognostic factors (i.e., ADT failure status, region, and concomitant use of corticosteroids at baseline for the induction study, and clinical remission status at maintenance baseline, concomitant use of corticosteroids at maintenance baseline, and induction treatment for the maintenance study). Overall, the baseline demographic and disease characteristics appeared to be reasonably balanced between treatment groups in both studies. For the induction study, patients were eligible and enrolled if they had a baseline MMS of 4 to 9, and those with a baseline MMS of 4 were capped at 5% or less. However, according to the sponsor, the statistical analysis plan was amended per “health authority request” (on April 26, 2022, after patient enrolment) for the primary efficacy and safety analyses to include patients who were randomized and treated, with a baseline MMS of 5 to 9. As a result, a total of 34 patients with a baseline MMS of 4 were excluded from the FAS primary efficacy and safety analyses, which could have compromised randomization. In general, the CDA-AMC review team and the clinical experts consulted by CDA-AMC did not consider this exclusion to have an important impact on study results, given that patient characteristics appeared to be balanced between the treatment groups, and the findings of the supplementary analyses that included those with an MMS of 4 were consistent with the primary analyses. Overall, the statistical methods used in both studies were appropriate. The studies were powered on their primary and key secondary outcomes between the treatment groups. The subgroup analyses were likely underpowered to identify subgroup differences. An appropriate method for adjusting for multiplicity was used for the primary and secondary outcomes, but there was no multiplicity control for IBDQ-defined remission and the subgroup analyses. The sponsor noted that, based on feedback from the FDA, IBDQ-defined remission was not included in the US-specific hierarchal testing procedure. Rates of study discontinuation were generally low in both studies and similar between groups, although in the induction study the rate in the placebo group (12.9%) was higher than the guselkumab group (5.5%), mostly attributed to withdrawal by patients. Nonresponder imputation was

used for missing data in the primary analysis and preplanned sensitivity analyses were done under different assumptions, which were considered appropriate by the CDA-AMC review team.

In general, the study populations aligned with the proposed Health Canada indication and reimbursement request, except that the proposed indication is not limited to patients who have had an inadequate response or who are unable to tolerate conventional or advanced therapy. The clinical experts did not consider the broader proposed indication to affect the generalizability of the findings from the induction and maintenance studies. The dosing and administration of guselkumab were consistent with the proposed product monograph. According to the clinical experts, the patient eligibility criteria and baseline characteristics of both studies were generalizable to adults with moderately to severely active UC in the Canadian setting. There were 8 patients in Canada included in the induction study and 6 patients in Canada included in the maintenance study. There was a relatively high screening failure rate in the induction study (269 out of 1,005 patients were screened out), mainly due to failure to meet eligibility criteria. The clinical experts did not regard the screening failures as factors that might influence the generalizability of studies' results. The studies included outcomes that were important to patients and clinicians, including clinical remission, clinical response, corticosteroid-free clinical remission, and HRQoL.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CDA-AMC's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., if the clinical importance was unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for clinical remission, endoscopic healing, clinical response and maintenance of clinical response, corticosteroid-free clinical remission, and HRQoL measured via IBDQ remission were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- remission and response (clinical remission, endoscopic healing, clinical response and maintenance of clinical response, and corticosteroid-free clinical remission)
- HRQoL (IBDQ remission).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for guselkumab versus placebo.

Table 3: Summary of Findings for Guselkumab vs. Placebo for Patients With Moderately to Severely Active Ulcerative Colitis – Induction and Maintenance Studies

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)					Certainty	What happens
		Placebo	Guselkumab 200 mg IV (induction)	Guselkumab 100 mg SC (maintenance)	Guselkumab 200 mg SC (maintenance)	Difference		
Clinical remission (FAS population)								
Proportion of patients with clinical remission Follow-up: 12 weeks (induction study)	701 (1 RCT)	79 per 1,000	226 per 1,000 (186 to 266)	NA	NA	149 more per 1,000 (99 more to 199 more)	High[a]	Guselkumab induction treatment results in a clinically important increase in clinical remission at 12 weeks when compared to placebo.
Proportion of patients with clinical remission Follow-up: 44 weeks (maintenance study)	568 (1 RCT)	189 per 1,000	NA	452 per 1,000 (381 to 523)	500 per 1,000 (429 to 571)	**100 mg SC:** 252 more per 1,000 (164 more to 339 more) **200 mg SC:** 295 more per 1,000 (209 more to 381 more)	High[a]	Guselkumab maintenance treatment results in a clinically important increase in clinical remission at 44 weeks when compared to placebo.
Endoscopic healing (FAS population)								
Proportion of patients with endoscopic healing Follow-up: 12 weeks (induction study)	701 (1 RCT)	111 per 1,000	268 per 1,000 (226 to 311)	NA	NA	160 more per 1,000 (105 more to 214 more)	High[b]	Guselkumab induction treatment results in an increase in endoscopic healing at 12 weeks when compared to placebo.

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)					Certainty	What happens
		Placebo	Guselkumab 200 mg IV (induction)	Guselkumab 100 mg SC (maintenance)	Guselkumab 200 mg SC (maintenance)	Difference		
Proportion of patients with endoscopic healing Follow-up: 44 weeks (maintenance study)	568 (1 RCT)	189 per 1,000	NA	495 per 1,000 (423 to 566)	516 per 1,000 (445 to 587)	**100 mg SC:** 295 more per 1,000 (207 more to 383 more) **200 mg SC:** 311 more per 1,000 (225 more to 398 more)	High[c]	Guselkumab maintenance treatment results in a clinically important increase in endoscopic healing at 44 weeks when compared to placebo.
Clinical response (FAS population)								
Proportion of patients with clinical response Follow-up: 12 weeks (induction study)	701 (1 RCT)	279 per 1,000	615 per 1,000 (569 to 662)	NA	NA	338 more per 1,000 (269 more to 407 more)	High[a]	Guselkumab induction treatment results in a clinically important increase in clinical response at 12 weeks when compared to placebo.
Proportion of patients with clinical response Follow-up: 44 weeks (maintenance study)	568 (1 RCT)	432 per 1,000	NA	777 per 1,000 (717 to 836)	747 per 1,000 (686 to 809)	**100 mg SC:** 336 more per 1,000 (245 more to 427 more) **200 mg SC:** 307 more per 1,000 (215 more to 400 more)	High[a]	Guselkumab maintenance treatment results in a clinically important increase in clinical response at 44 weeks when compared to placebo.

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)					Certainty	What happens
		Placebo	Guselkumab 200 mg IV (induction)	Guselkumab 100 mg SC (maintenance)	Guselkumab 200 mg SC (maintenance)	Difference		
Corticosteroid-free clinical remission (FAS population)								
Proportion of patients with corticosteroid-free clinical remission Follow-up: 44 weeks (maintenance study)	568 (1 RCT)	184 per 1,000	NA	452 per 1,000 (381 to 523)	489 per 1,000 (418 to 561)	**100 mg SC:** 257 more per 1,000 (170 more to 345 more) **200 mg SC:** 290 more per 1,000 (205 more to 376 more)	High[d]	Guselkumab maintenance treatment results in a clinically important increase in corticosteroid-free clinical remission at 44 weeks when compared to placebo.
IBDQ remission (FAS population)								
Proportion of patients with IBDQ remission Follow-up: 12 weeks (induction study)	701 (1 RCT)	296 per 1,000	513 per 1,000 (465 to 561)	NA	NA	219 more per 1,000 (149 more to 290 more)	High[a]	Guselkumab induction treatment results in a clinically important increase in IBDQ-defined remission at 12 weeks when compared to placebo.
Proportion of patients with IBDQ remission Follow-up: 44 weeks (maintenance study)	568 (1 RCT)	374 per 1,000	NA	644 per 1,000 (575 to 712)	642 per 1,000 (574 to 710)	**100 mg SC:** 263 more per 1,000 (168 more to 357 more) **200 mg SC:** 259 more per 1,000 (165 more to 354 more)	High[a]	Guselkumab maintenance treatment results in a clinically important increase in IBDQ remission at 44 weeks when compared to placebo.

CI = confidence interval; FAS = full analysis set; IBDQ = Inflammatory Bowel Disease Questionnaire; NA = not applicable; RCT = randomized controlled trial; SC = subcutaneous; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]For clinical remission, clinical response, and IBDQ remission, a between-group absolute risk difference of 7.5% and 10% (75 and 100 fewer or more events per 1,000 patients) at 12 weeks and 44 weeks, respectively, were clinically important, according to the clinical experts. The point estimate and entire CI exceeded the threshold.

[b]For endoscopic healing at 12 weeks, the clinical experts could not determine a minimal important difference, so the target of certainty appraisal was any effect. The point estimate and entire CI exceeded the null in favour of guselkumab.

[c]For endoscopic healing at 44 weeks, a between-group absolute risk difference of 10% (100 fewer or more events per 1,000 patients) was clinically important, according to the clinical experts. The point estimate and entire CI exceeded the threshold.

[d]For corticosteroid-free clinical remission at 44 weeks, a between-group absolute risk difference of 15% (150 fewer or more events per 1,000 patients) was clinically important, according to the clinical experts. The point estimate and entire CI exceeded the threshold.

Source: QUASAR Induction and Maintenance Clinical Study Reports. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

One NMA was submitted by the sponsor to inform the pharmacoeconomic model and to fill gaps in the comparative evidence for other treatments of interest for moderately to severely active UC.

Description of Studies

A feasibility assessment was undertaken to ascertain the extent of clinical heterogeneity across the trials identified in the systematic literature review. Trial design characteristics, patient eligibility criteria, baseline patient characteristics, outcome characteristics (i.e., definitions and methods of reporting outcomes), and placebo response were considered sources of clinical heterogeneity and explored in the feasibility assessment. Based on the feasibility assessment, an NMA was used for the outcomes of clinical remission and clinical response for induction and maintenance (1 year). The NMA assessed the induction and maintenance treatment effects of guselkumab versus adalimumab, infliximab, tofacitinib, upadacitinib, mirikizumab, vedolizumab, etrasimod, ozanimod, and ustekinumab for the treatment of adults with moderately to severely active UC. Some comparators were not relevant to Canadian public payers (e.g., risankizumab, filgotinib) and were therefore excluded from this report. A Bayesian NMA was conducted as the primary analysis of outcomes using an ordinal regression model to estimate odds ratios (ORs) and 95% credible intervals. Random-effects NMA results were summarized based on 2 distinct patient populations: those with ADT failure and ADT nonfailure for both induction and maintenance therapy. The model fit of the induction results was adjusted by a baseline response due to placebo, but it was not possible to fit the same model in the maintenance phase (1-year analysis); therefore, the presented results are unadjusted.

Efficacy Results

The results for clinical remission at induction in the ADT nonfailure population did not favour any particular treatment (i.e., 95% credible intervals crossed the null), and the results for the ADT failure population favoured upadacitinib versus guselkumab 200 mg. For clinical remission at maintenance in the ADT nonfailure population, the results favoured guselkumab 200 mg versus adalimumab and golimumab, and the results for the ADT failure population showed no difference between treatments. The results for clinical response at induction in the ADT nonfailure population favoured guselkumab 200 mg versus golimumab and adalimumab, and the results for the ADT failure population favoured guselkumab versus adalimumab. For

clinical response at maintenance in the ADT nonfailure population, the results favoured guselkumab 100 mg and 200 mg versus adalimumab, and the results for the ADT failure population showed no difference between treatments.

There were several notable sources of heterogeneity for potential effect modifiers across the included studies. These included trial design characteristics, patient eligibility criteria, baseline patient characteristics, and definitions and methods of reporting outcomes. In addition, beyond the induction phase, the authors noted that although placebo is a common comparator across the majority of included trials, placebo groups across rerandomized studies may not be equivalent due to variation in treatments received during the preceding induction phase. The magnitude and direction of potential bias due to heterogeneity on outcome estimates cannot be predicted.

Harms Results

Harms were not assessed in the NMA.

Critical Appraisal

The methods used to conduct the systematic literature review and NMA were prespecified with an a priori protocol, and used appropriate criteria to search databases, select studies, extract data, and assess risk of bias of the included studies. Selection bias is expected to be low given the comprehensiveness of the searches and methods for study selection. The NMA included relevant outcomes identified by the CDA-AMC team (clinical remission and clinical response); however, clinically relevant and patient-relevant outcomes such as endoscopic healing, corticosteroid-free clinical remission, HRQoL, and harms were not included in the comparisons. The majority of comparators within the evidence network were informed by a single study, resulting in a star-shaped network and limiting certainty in the assumptions of the analysis.

Heterogeneity was noted across the studies, and while the metaregression random-effects model accounts for some heterogeneity, there is a risk of the exchangeability assumption being validated (specifically, potential effect modifiers across the included studies that could not be controlled for). Identified variables of concern included trial design characteristics, patient eligibility criteria, baseline patient characteristics, and outcome characteristics (i.e., definitions and methods of reporting outcomes). Variations in placebo effect estimates across studies support these concerns about heterogeneity as well as possible violations of the assumptions of transitivity for the NMA. In addition, beyond the induction phase, the authors noted that although placebo is considered to be a common comparator across the majority of included trials, placebo arms across rerandomized trials may not be equivalent due to variation in treatments received during the preceding induction phase. In particular, carry-over effects observed due to previous treatments are likely to vary based upon treatment mechanism, potentially constituting a substantial source of cross-trial heterogeneity, which is evidenced in part by variations in baseline risk across included trials.

The specified model, while referred to as ordinal regression, is a multinomial regression that removes correlations between the outcomes of response and remission and estimates an OR for each outcome individually against no response or remission. Furthermore, the model structures the data such that the response outcome has a different definition from the clinical trial setting, defined as response without

remission. This redefinition introduces a core issue: the response outcome is defined conditionally on a separate outcome that can occur at a future date, and whether an improvement in response rate due to treatment is a benefit or a harm becomes unclear. Ultimately, the interpretation of the ordinal OR when the model assumptions are violated can create a misleading impression of how the outcomes and treatments are related. Due to the limitations in the NMA, the relative treatment effects of guselkumab versus other relevant comparators is uncertain, and there is no conclusive evidence of a preferred treatment based on the reported results.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies were submitted by the sponsor.

Conclusions

Evidence from 2 phase III, double-blind RCTs (the QUASAR induction and maintenance studies) reported on outcomes that were important to both patients and clinicians. The studies showed high certainty of evidence that treatment with guselkumab results in a clinically meaningful increase in clinical remission, endoscopic healing, clinical response and maintenance of clinical response, corticosteroid-free clinical remission (maintenance only), and HRQoL via IBDQ remission at 12 weeks in the induction trial and 44 weeks in the maintenance trial compared to placebo, in adults with moderately to severely active UC. Although the proposed Health Canada indication is broader than the patient populations enrolled in the studies (i.e., patients who had experienced an inadequate response to or were unable to tolerate conventional or advanced therapy), the clinical experts consulted by CDA-AMC did not consider the proposed indication to affect the generalizability of the findings. There were no new safety signals identified and the safety of guselkumab was consistent with the known safety profile the drug. Due to limitations of the indirect treatment comparison, mostly attributed to the heterogeneity across studies, no conclusions can be drawn on the relative efficacy and safety of guselkumab versus other relevant comparators.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by a Markov model
Target population	Adult patients with moderately to severely active UC who have experienced an inadequate response to or failure to tolerate conventional therapy[a] (ADT-naive subgroup) or ADT[b] (ADT-experienced subgroup)
Treatment	Guselkumab

Component	Description
Dose regimen	200 mg by IV in week 0, week 4, and week 8 followed by 100 mg by SC injection at week 16 and 100 mg every 8 weeks thereafter. A dose of 200 mg administered by SC injection at week 12 and every 4 weeks thereafter may be considered for patients who do not show adequate therapeutic response to guselkumab, or according to clinical judgment.
Submitted price	Guselkumab: $3,059.74 per 100 mg/mL prefilled syringe or patient-controlled injector Guselkumab: $3,059.74 per 200 mg/2 mL prefilled syringe or prefilled pen Guselkumab: $3,059.74 per 200 mg/20 mL vial for IV infusion
Submitted treatment cost	$32,252 in year 1 and $29,995 annually thereafter, assuming 49.7% of patients receive the lower maintenance dose (i.e., 100 mg every 8 weeks)
Comparators	• Adalimumab • Conventional therapy[a] • Etrasimod • Golimumab[c] • Infliximab[c] • Mirikizumab • Ozanimod • Tofacitinib • Upadacitinib • Ustekinumab • Vedolizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (58 years)
Key data sources	Sponsor-submitted NMA in which the efficacy for guselkumab was informed by QUASAR
Key limitations	• The comparative efficacy and safety of guselkumab relative to other biologics available for moderately to severely active UC is uncertain due to a lack of head-to-head evidence and limitations with the sponsor's NMAs, which precluded the CDA-AMC clinical review from being able to draw conclusions regarding the relative efficacy and safety of guselkumab. • The relevance of conventional therapy as a comparator was uncertain, as very few patients are expected not to receive an ADT and the entry of guselkumab is not expected to impact the proportion of patients who are receiving conventional therapy. Further, in the ADT-experienced population, infliximab and golimumab were not included as comparators in the pharmacoeconomic analysis, owing to a lack of data; however, according to clinical expert feedback and drug plan input received for this review, both comparators are deemed to be relevant in this patient population. • The proportion of patients receiving guselkumab 200 mg vs. 100 mg was not aligned between the sponsor's pharmacoeconomic analysis and BIA, introducing uncertainty regarding the drug acquisition cost for guselkumab. In addition, the proportion of patients receiving high doses of several comparators was lower than anticipated, based on clinical expert feedback received for this review, meaning costs for some comparators may be underestimated in the sponsor's analysis. Neither assumption is expected to change overall conclusions regarding cost-effectiveness of guselkumab.
CDA-AMC reanalysis results	There is insufficient clinical evidence to justify a price premium for guselkumab relative to currently available treatments for moderately to severely active UC who have an inadequate response or failure to tolerate conventional therapy or ADT.

ADT = advanced therapy; BIA = budget impact analysis; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; SC = subcutaneous; UC = ulcerative colitis; vs. = versus.

[a]Conventional therapy is assumed to comprise azathioprine, 6-mercaptopurine, methotrexate, 5-aminosalicylate, prednisone, and budesonide.
[b]ADT is assumed to be comprised of anti-TNFs (adalimumab, infliximab, and golimumab), vedolizumab, or tofacitinib.
[c]Not included as a comparator in the ADT-experienced subgroup due to a lack of clinical data.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: drug acquisition costs are highly uncertain owing to the proportion of patients receiving the higher maintenance dose for applicable treatments and the dosages received in clinical practice; the full Health Canada population was not modelled, as the sponsor restricted the budget impact analysis to patients eligible for advanced therapy; public coverage rates are uncertain and the sponsor's value could not be validated; and the market uptake of guselkumab may be underestimated.

In the absence of more reliable estimates to inform the key parameters of the budget impact analysis (i.e., dose mix, market shares, public coverage rates, and market uptake), the sponsor's submitted base case was maintained.

The 3-year budget impact of reimbursing guselkumab for adult patients with moderately to severely active UC who are eligible for ADT is projected to be $10,194,289 (year 1: $863,116; year 2: $3,649,218; year 3: $5,681,955).

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed

Meeting date: March 26, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.